HEMATALOGICAL ABNORMALITIES IN ALCOHOLICS

Dissertation submitted for

MD DEGREE (BRANCH 1) GENERAL MEDICINE

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MEDICAL UNIVERSITY

CHENNAI – tamil nadu

CERTIFICATE FROM THE DEAN

This is to certify that this dissertation entitled "**HEMATOLOGICAL ABNORMALITIES IN ALCOHOLICS"**is the bonafide work of **Dr.P.THIRUNAVUKARASU** in partial fulfillment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for M.D General Medicine Branch I examination to be held in **April 2017.**

Dr.M.R.VAIRAMUTHU RAJU.,MD.

THE DEAN,

Madurai Medical College,

Madurai.

CERTIFICATE FROM THE HOD

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DR.V.T.PREM KUMAR,M.D.,

Professor and HOD,

Department Of General Medicine,

Government Rajaji Hospital,

Madurai Medical College,

Madurai.

CERTIFICATE FROM THE GUIDE

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DR.M.NATARAJAN,M.D.,

Professor of Medicine ,

Department Of General Medicine,

Government Rajaji Hospital,

Madurai Medical College,

Madurai

DECLARATION

I Dr.P.THIRUNAVUKARASU declare that, I carried out this work on"**HEMATOLOGICAL ABNORMALITIES IN ALCOHOLICS''''** at the Department of Medicine, Govt. Rajaji Hospital during the period **NOVEMBER 2015 TO APRIL 2016**. I also declare that this bonafide work or a part of this work was not submitted by me or any others for any award, degree or diploma to any other University, Board either in India or abroad.

This dissertation is submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulations for the award of **M.D Degree General Medicine Branch- I**; examination to be held in **April 2017.**

Place : Madurai **Dr.P.THIRUNAVUKARASU**

Date :

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INTRODUCTION

“Alcohol consumption has increased considerably in the past 25 years,the need for accurate methods for detection and monitoring of alcohol related problems in different health care settings is clearly considerable.Despite such a need, there is no exact clinical finding or symptom in a patient history,that is sufficiently sensitive and specific to detect alcohol related problem in its early phase.”

“The clinical signs of alcohol abuse are rather minimal in the early phase of this process while most of the signs arise later after several years of excessive drinking. Also alcohol consumption is usually under-reported in interviews; alcohol abusers tend to underestimate their drinking even more than the social drinkers.The reasons for using biological laboratory markers are that they give objective information about alcohol consumption and changes in drinking habits. Among these laboratory markers haematological abnormalities appear earlier than biochemical abnormalities & also reversible with abstinence.”

“Alcohol effect on hematopoeitic system are both direct & indirect, its also dose dependent, The direct consequences of excessive alcohol consumption include toxic effects on the bone marrow; suppress the production of all blood cell precursors. Alcohol’s indirect effects include”

“nutritional deficiencies that impair the production and function of various blood cells. Among the hematological abnormalities, increased MCV values have been observed in 64-89% of alcohol abusers.Increased MCV values are also found in cases of vitamin B12 and folic acid deficiency, liver diseases, several hematological disorders,hypothyroidism,in users of anti-epileptics. Alcohol abuse has been found to explain increased MCV values in 89% of men and 56% of women in general practice .MCV return to normal after 3 months of abstinence.”

“One of the recently developed routine laboratory tests for alcohol abuse is serum carbohydratedeficient transferrin (CDT). This marker consists of the asialo, mono-sialo and di-sialo isoforms of transferrin that are deficient in their terminal trisaccharides. CDT measurement has a sensitivity of 82% and specificity of 97%. False-positives have been reported in patients with severe liver diseases (mainly in primary biliary cirrhosis, chronic hepatitis C, hepatic malignancies). During abstinence,the CDT values normalize with a mean half-life of 14-17 days.”

“CDT has now been shown to have a high specificity and a sensitivity that is at least equal to that of the conventional laboratory markers. CDT values seem to increase after 10 days of drinking at alevel”

“of 50-80 g ethanol per day. It also has a relatively good correlation with self-reported alcohol consumption, but not with conventional markers.”

“Decision making about the role of alcohol as an etiological factor for these abnormalities & in motivating patients to change their drinking habits by demonstrating the reversal of these abnormalitiesafterabstinence.These hematological abnormalities can be used as a marker of detection of alcohol abuse and for monitoring either abstinence or relapse during treatment.”

AIMS AND OBJECTIVES

"TO INVESTIGATE THE ALTERATIONS OF HEMATOLOGICAL MARKERS IN A POPULATION OF ALCOHOL DEPENDENT INDIVIDUALS SINCE THE NEED FOR SENSITIVE BIOLOGICAL MARKERS TO DETECT AND PROVE RECENT DRINKING HAS BEEN THE FOCUS OF MANY RESEARCH GROUPS"

REVIEW OF LITERATURE

ALCOHOLISM

“Worldwide, alcohol consumption is increasing. This is particularly notable in the UK where average alcohol consumption has more than doubled in the last 50 years. The association of alcohol with cirrhosis was recognizedby Matthew Baillie in 1793. In recent years, alcohol consumption has correlated closely with deaths from cirrhosis. Cirrhosis mortality has risen dramatically in the UK , where alcohol - related liver disease is now the fourth commonest cause of death in the under 65s.”

“There are different types of alcohol. Some are used in chemistry laboratories and industry, e.g.isopropyl and methyl alcohol. Isopropanol, or isopropyl alcohol is also used in industrial processes as well as in home cleaning products and skin lotions. It is also commonly known as "rubbing alcohol". Methanol,or methyl alcohol or wood alcohol has been used as an industrial solvent and is also commonly available as methylated spirit. It is found in cleaning solvents, paint removers, photocopier developer and anti-freeze solutions. As such, it is often available in large quantities inexpensively. It is similar to ethanol but the end product after it is digested by the body is formaldehyde, which is poisonous. This is responsible for” "alcohol poisoning".

”Methanol poisoning leading to blindness has been known to occur on consuming even small amounts.”

“Another type of alcohol is ethyl alcohol, also known as ethanol. This has been consumed by human beings for its intoxicating and mind-altering effects. The term 'alcohol', unless specified otherwise, refers to ethanol or ethyl alcohol. It is a thin, clear liquid with harsh burning taste and high volatility. It is usually consumed in diluted concentrations of absolute (i.e. 100 per cent) ethyl alcohol. Ethyl alcohol is also used as a reagent in some industrial applications. For such use, ethyl alcohol is combined with small quantities of methanol, with the mixture being called” "denatured ethanol" “to prevent theft for human consumption.”

Brief description of alcoholic beverages:

“Wines are made from a variety of fruits, such as grapes, peaches, plums or apricots. The most common wines are produced from grapes. The soil in which the grapes are grown and the weather conditions in the growing season determine the quality and taste of the grapes which in turn affects the taste and quality of wines. When ripe, the grapes are crushed and fermented in large vats to produce wine”.

“Beer is also made by the process of fermentation. A liquid mix, called wort, is prepared by combining yeast and malted cereal, such as

corn, rye, wheat or barely.Fermentation of this liquid mix produces alcohol and carbon dioxide. The process of fermentation is stoppedbefore it is completed to limit the alcohol content. The alcohol so produced is called beer. It contains 4 to 8 per cent of alcohol".

"Whisky is made by distilling the fermented juice of cereal grains such as corn, rye or barley. Scotch whisky was originally made in Scotland. The word "Scotch" has become almost synonymous with whisky of good quality."

"Rum is a distilled beverage made from fermented molasses or sugarcane juice and is aged for at least three years. Caramel is sometimes used for colouring. Brandy is distilled from fermented fruit juices. Brandy is usually aged in oak casks. The colour of brandy comes either from the casks or from caramel that is added."

"Gin is a distilled beverage. It is a combination of alcohol, water and various flavours. Gin does not improve with age, so it is not stored in wooden casks."

"Liqueurs are made by adding sugar and flavouring such as fruits, herbs or flowers to brandy or to a combination of alcohol and water. Most liqueurs contain 20-65 per cent alcohol. They are usually consumed in small quantities after dinner."

Types of alcoholic beverages

Types of alcoholic beverages

Beverage	Source	Alcohol content (percentage)
Brandy	Fruit juices	40 - 50
Whisky	Cereal grains	40 - 55
Rum	Molasses/sugarcane	40 - 55
Wines (Port, Sherry, Champagne, etc)	Grapes (also other fruits)	10 - 22
Beer	Cereals	4 - 8

"Common local brews in the countries of the South-East Asia Region"

"Arrack is a distilled beverage, obtained from paddy or wheat. Jaggery, sugar or sugarcane is added to either of these two cereals and boiled with water. This is allowed to ferment, after which it is distilled. This beverage contains about 50- 60 per cent of alcohol."

"Toddy is obtained from the flowers of a coconut or palm tree. A white liquid, with a sweetish taste, oozes out of these flowers. When consumed fresh, this juice has no intoxicating effect. This liquid is collected and allowed to ferment. At times, yeast is added to hasten"

“theprocess.The fermented juice has an alcohol content of approximately 5-10 percent”

Types of local brews in the countries of the South-East Asia Region

Country	Local brews
Bangladesh	Bangla Mad, Cholai, Tari
Bhutan	Ara
India	Arrack, Desi Sharab, Tari, Tharra
Indonesia	Palm wine
Nepal	Raksi, Tadi, Chayang, Tomb
Sri Lanka	Toddy, Arrack
Thailand	Oou, Krachae, Namtanmao, Sartha, Waark

Equivalence of different beverages

“The volume-by-volume strength of alcoholic beverages varies considerably. The equivalence of different beverages is measured in terms of 'units' of alcohol. One unit is equal to approximately 10 grams of absolute alcohol, often considered as one drink, since it is available from 30ml (1fluid ounce or small peg) of spirits like whisky, rumor brandy.

The same amount of alcohol, one unit, is also available from a glass of wine, which is generally 120 ml or half a pint or 285 ml of beer.Total estimated alcohol consumption in a country in a given year.The total estimated alcohol consumption in a country in a given year can be calculated by adding all the alcohol produced in the country and the”

“alcohol imported, and then subtracting the alcohol exported from the country.”

ALCOHOL METABOLISM

ABSORPTION AND DISTRIBUTION

“Alcohol is absorbed from the gastrointestinal tract bysimple diffusion and peak blood alcohol concentrations are reached after 20 minutes. Most of the absorptionoccurs in the duodenum and upper jejunum. The rate of absorption is delayed following a meal and increases in proportion to the alcohol concentration of the drink consumed. Alcohol distribution is dependent on blood flow, with vascular organs such as the brain rapidly equilibrating with plasma levels. Alcohol is poorly soluble in lipids, possibly explaining the higher plasma concentrationsfound in”

“females compared to males that have consumedthe same amount of ethanol.”

“Alcohol cannot be stored and obligatory oxidation must take place, predominantly in the liver. The healthy individual cannot metabolize more than 160 – 180 g/day.Alcohol induces enzymes used in its catabolism, and thehazardous drinker, at least while the liver is relatively unaffected, can metabolize more”.

“Symptoms at different levels of blood alcohol concentration”

BAC	Symptoms
<50 mg/dL	Some impairment in motor coordination and thinking ability Talkativeness Relaxation
50-150 mg/dL	Altered mood (increased well-being or unhappiness) Friendliness, shyness or argumentativeness Impaired concentration and judgement Sexual disinhibition
150-250 mg/dL	Slurred speech Unsteady walking Nausea Double vision Increased heart rate Drowsiness Mood, personality and behaviour changes which may be sudden, angry and antisocial
300 mg/dL	Unresponsive/extremely drowsy Speech incoherent/confused Memory loss Vomiting Heavy breathing
>400 mg/dL	Breathing slowed, shallow or stopped Coma Death

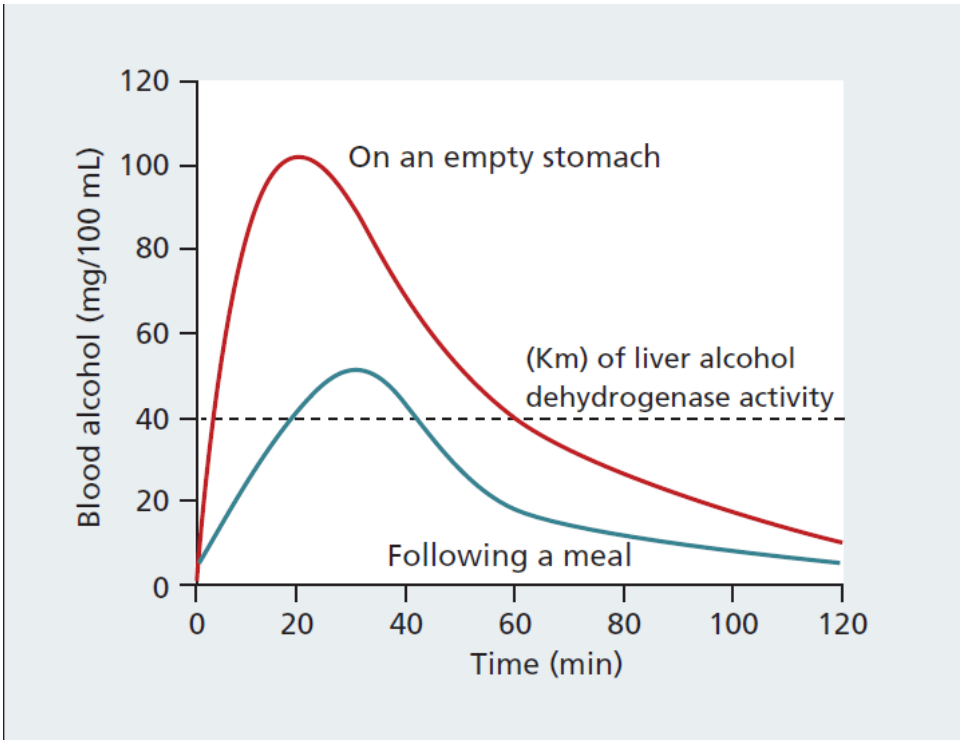
Alcohol to acetaldehyde

“Between 80 and 85% of ethanol oxidation is by initial conversion to acetaldehyde catabolized by alcohol dehydrogenase (ADH). This takes place in the cytosol. The resulting increase in the ratio of NADH/NAD, which is further increased by acetaldehyde oxidation,is partly responsible for the metabolic imbalances that occur following alcohol ingestion and has been considered to play a major role in the initial pathogenesis of alcohol - induced fatty liver.”

“Most of the remaining ethanol is metabolized by the microsomal ethanol - oxidizing system (MEOS) pathway, an accessory pathway that principally involves a specific alcohol - inducible form of cytochrome P450, designated CYP2E1 . The induction of CYP2E1 in hazardous drinkers may explain their increased susceptibility to hepatotoxicity by other drugs that are converted to toxicmetabolites by this enzyme system. An important example of this phenomenon is the increased susceptibility to the toxic effects of paracetamol (acetaminophen),where severe liver damage has been reported in dependent drinkers taking therapeutic doses. Acetaldehyde to acetate”

“Most of the acetaldehyde formed from ethanol oxidation is further oxidized in the liver to acetate by aldehyde dehydrogenases (ALDHs). Acetate may be oxidized to carbon dioxide and water, or converted by the citric acid cycle to other compounds, including fatty acids. The inactive”

“form of ALDH (ALDH2*2) is present in about 50% of Orientals. The accumulation of acetaldehyde may account for the flushing seen with alcohol consumption in homozygotes”



Pathogenesis of steatosis

“The accumulation of triacylglycerol (TAG) within theliver is an early and reversible effect of alcohol consumption.Alcohol increases peripheral lipolysis and thealtered liver redox potential increases fatty acid synthesis.This increase in substrate supply (glycerol and freefatty acids) enhances the rate of esterification, resultingin TAG accumulation. This is compounded by thealcohol - induced inhibition of the enzyme which controls TAG export from the liver, microsomal triglyceridetransfer protein (MTP).”

Oxidative stress and lipid peroxidation

“In alcohol - related liver disease (ALD) the generation ofpro - oxidants overwhelms the endogenous antioxidantsystems, resulting in lipid peroxidation. These pro -oxidants can come directly from ethanol metabolism orfrom activated phagocytes. Liver injury is compoundedby the depletion of endogenous cellular, particularlymitochondrial, antioxidants in hazardous drinkers.”

Acetaldehyde

“Acetaldehyde is generated by both ADH and the MEOSsystems and may account for many of the features ofacute alcoholic hepatitis. Acetaldehyde isextremely reactive and toxic; it binds to phospholipids,amino acid residues and sulphydryl groups. It canproduce altered surface antigens and depolymerize proteins,altering their folding. When abnormally folded orunfolded proteins build up in the endoplasmic reticulum(ER), this results in a phenomenon known as ‘ ERstress ’. ER stress induces further lipid synthesis, antioxidant depletion and ultimately apoptosis.”

Endotoxin and cytokines

“A complex relationship exists between endotoxin,Kupffer cell activation and the release of cytokines andchemokines. Endotoxin is increased in the blood of hazardous drinkers . This is related to increased”

“intestinal bacterial flora, increased gut permeability andreduced endotoxin scavenging by the reticuloendothelialsystem . Endotoxin results in the release ofcytokines and reactive oxygen species from Kupffercells. In alcoholic hepatitis, tumour necrosis factor - α(TNF - α) and interleukin - 8 (IL - 8) production are particularly increased .The biological effects of certain cytokines resemblethe clinical and histological manifestations of ALD. TNF - α can induce steatosis, the productionof reactive oxygen species (ROS) and hepatocyte apoptosis.IL - 8 is involved in the recruitment and activationof neutrophils.”

Immunological liver damage

“Protein adducts formed from ethanol metabolites andhost proteins can act as neoantigens to incite humoralB - cell and cytotoxic T - cell lymphocyte responses inALD. Antibodies can be shown against acetaldehydeprotein adduct - derived epitopes andhydroxyethyl radical – CYP2E1 adducts . Antibodies can also be seen to native CYP2E1, suggesting that autoimmunemechanisms may play a role in alcohol - related liver disease. “

“The true importance of immunologicalmechanisms is not clear as they may represent an epiphenomenonwhereby immune responses are generatedto proteins released from hepatocytes damaged throughother mechanisms.”

Alcohol and fibrosis

"The proliferation and activation of stellate cells in ALDis promoted by Kupffer cells and hepatocytes. Kupffercells induce collagen synthesis through the productionof transforming growth factor - β (TGF - β), TNF - α and ROS. Hepatocytes induce fibrosis through the productionof ROS or through apoptosis. TGF - β is producedwhen apoptotic hepatocytes are phagocytosed and thisin turn can activate stellate cells ."

Alcohol and cancer

"Alcohol consumption is associated with hepatocellularcarcinoma and several extrahepaticcancers.The mechanisms are likely to be related to lipid peroxidation and DNA mutagenesis, reduced DNA methylationand immunosuppression."

Susceptibility

Environmental factors

Dose of alcohol

"The average intake of alcohol in a large group of maledependent cirrhotic patients was 160 g/day for 8 years.The risk of developing ALD begins at 30 g/day ofEthanol but for most individuals the dose that confers a significant risk is greater than 80 g alcoholdaily. The duration of consumption is also important. Inone study, neither cirrhosis nor"

“alcoholic hepatitis wereseen in patients who consumed an average of 160 g ofethanol per day for less than 5 years, whereas 50% ofpatients consuming high levels of alcohol for an averageof 21 years developed cirrhosis . Liver injury appearsto be unrelated to the type of beverage; reports that winedrinkers have a lower risk than beer and spirit drinkersand that drinkers of mixed beverages have a higher riskthan those keeping to a single type of drink are probablyexplained by confounding lifestyle factors associatedwith particular drinking patterns. Continued dailyimbibing is more dangerous than intermittent consumptionwhen the liver is given the opportunity to recover;it is therefore recommended that individuals shouldhave at least two alcohol- free days per week.ALD and dependence do not necessarily go together.Those who develop alcohol - related liver damage areoften not dependent on alcohol. Most dependentpatients have normal liver function “.

Diet

“Cirrhosis mortality has been linked with diets high inpork (high in linoleic acid) consumption and unsaturated fats and low in carbohydrate . Obesity and associated hyperglycemia increase the incidence of allstages of ALD in heavy drinkers .”

Genetic factors

Gender

“Hazardous drinking is increasing among women owingto a decline in the social stigma and the increased availability of alcohol. Women are less likely to be suspectedof alcohol abuse; they present at a later stage, are more susceptible to liver injury and are more likely to relapseaftertreatment . This may be related to the reducedvolume of distribution of alcohol, or the fact that, inanimal models at least, oestrogen increases gut permeability to endotoxin. Women are more likely to progress from alcoholic hepatitis to cirrhosis even if they abstain”.

Non - gender - linked genetic factors

“Patterns of alcohol drinking are, at least partially, inherited;however, no specific genetic variants have been reproducibly associated with susceptibility in largestudies. Susceptibility to liver disease may also have an inherited component. Concordance rates for alcohol -related cirrhosis are three times higher in monozygotic than in dizygotic twin pairs . Alcohol – related liver damage is a polygenic disorder so multiple polymorphisms are likely to contribute. They are likelyto be in genes controllingfataccumulation,oxidative stress,endotoxin

– “mediated release of proinflammatorycytokines and immunological damage .”

Histological features

Fatty liver

“Fat (steatosis) accumulates predominantly in zones 3 and 2 although in the more severely affected, the fatty change is diffuse. Typically the fat is in a macrovesicular(large droplet) form although it can also be in a microvesicular”

“(small droplet) form.Large fat droplets appear in hepatocytes within daysof excess alcohol ingestion. Microvesicular fat probably reflects the presence of mitochondrial injury and resulting inhibition of fatty acid oxidation. In support, hepatic mitochondrial DNA deletion has been reported in patients with alcohol - related fatty liver. Fatty change can be quantified according to the proportion of hepatocytes that contain fat.”

Alcoholic hepatitis

“The full histological picture of a florid, acute alcoholichepatitis is relatively rare. Typical features include someor all of the following:*Ballooning degeneration.* Hepatocytes are swollen withgranular cytoplasm often dispersed into fine strands.The nucleus is” “

“small and hyperchromatic. The ballooningis due to retention of water and to failure of themicrotubular excretion of protein from the” hepatocyte.

Acidophilic bodies. These represent hepatocyteapoptosis.

Mallory – Denk bodies. These are seen on haematoxylinand eosin stained sections as purplish - red intracytoplasmicinclusions. They may be more obvious with

Masson’s trichrome or chromophobe aniline blue stains.They consist of clumped organelles — largely intermediate filaments — and may target the hepatocyte for

destruction. The Mallory - containing cell is surroundedby a satellite of polymorphs.

Giant mitochondria. These form globular intracytoplasmicinclusions seen by light microscopy using a Massontrichrome stain.

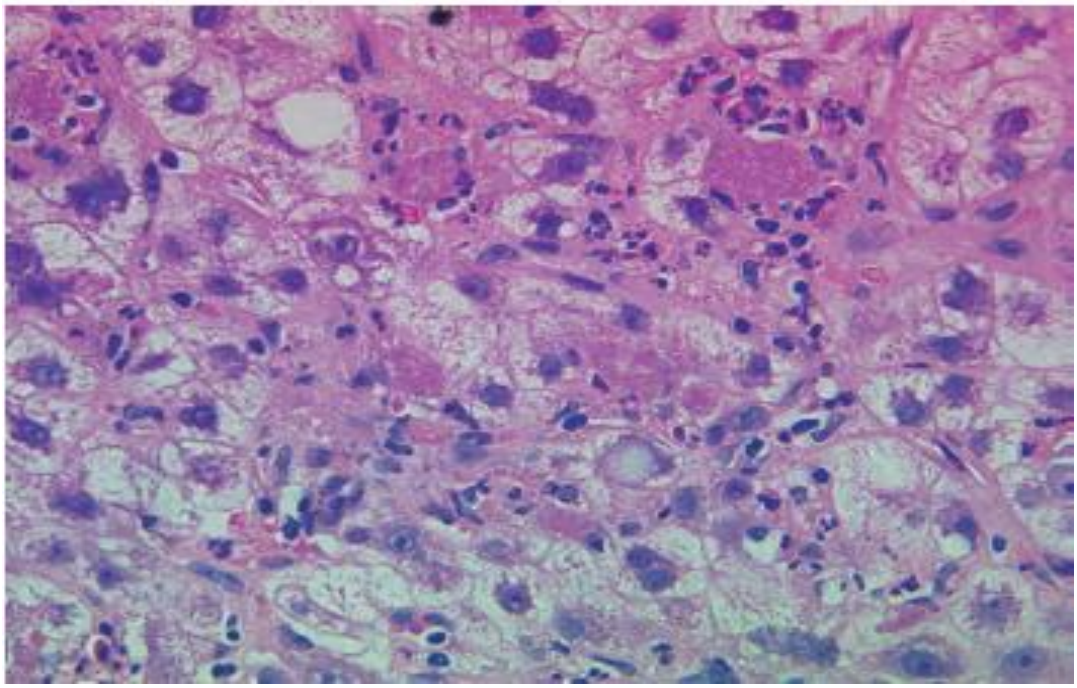
Fibrosis. Collagen deposition is usually maximal in zone”

“3. The fibres are perisinusoidal and enclose normal orballooned hepatocytes. The pericellular fibrosis is likelattice or chicken wire and has been termed ‘ creepingcollagenosis ’. Collagenization of the space of Disse is shown by electron microscopy and is associated with a reduction in the porosity of the sinusoidal lining . These changes interferewith the exchange of substances between plasma andthe hepatocyte cell membrane and contribute to portalhypertension. Associated lesions in”

“terminal and sublobularveins include lymphocytic phlebitis, gradualobliteration and eventual veno - occlusion.

Portal zone. Changes in the portal zone are inconspicuousand mild chronic inflammation is seen only in the advanced case. Zone 1 fibrosis if present is not nowthought due to previous pancreatitis .

Cholestasis. Cholestasis in bile canaliculi is a feature ofall types of alcohol - related liver disease. It is stronglyassociated with decreased survival”



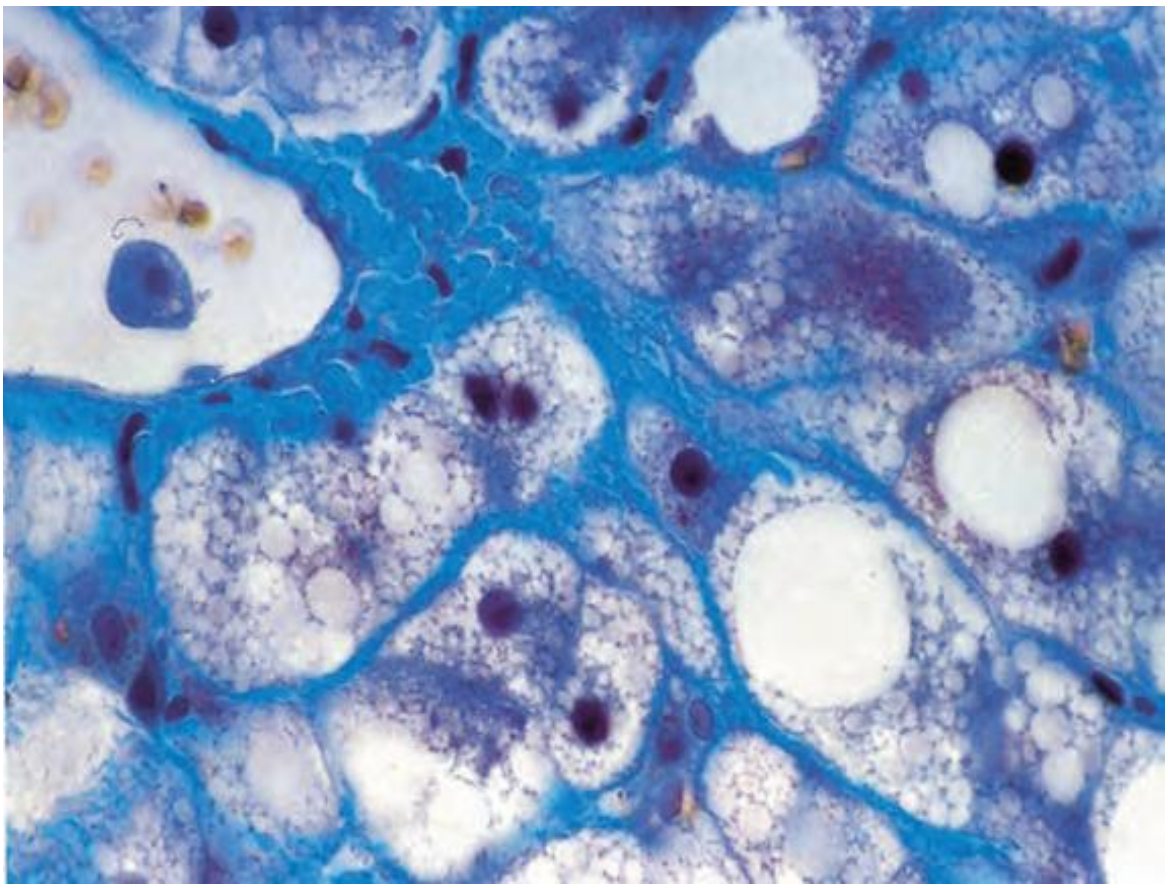
“IMAGE:Acute alcoholic hepatitis with ballooning degeneration, Mallory - Denkbodies and satellitosis (neutrophil polymorph infiltrate around hepatocytes)

These histological patterns form a spectrum fromminimal hepatitis to an advanced, probably irreversible picture, where necrosis is more”

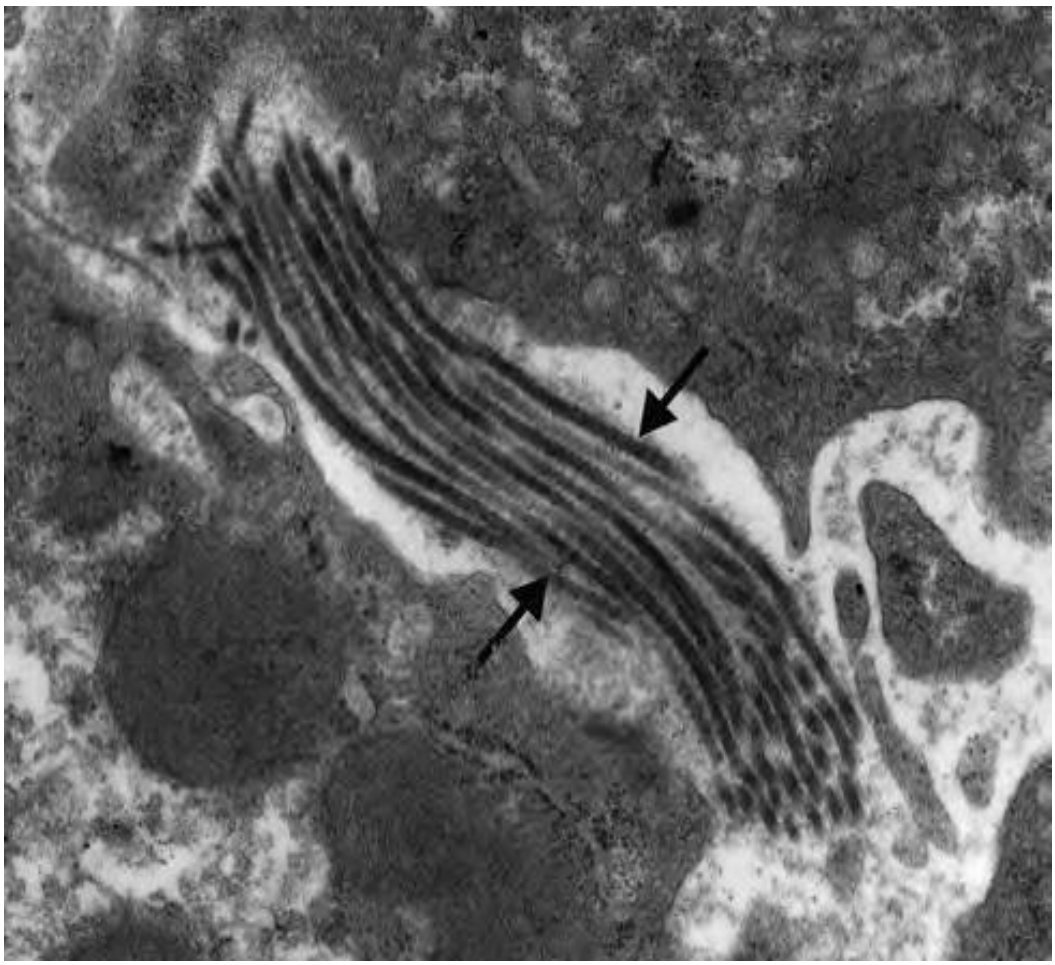
“extensive and fibrosis is prominent. Alcohol- related hepatitis is a precursor ofcirrhosis and in the majority of cases is superimposedon established cirrhosis.”

Cirrhosis

“Classical alcohol - related cirrhosis is micronodular. No normal zonal architecture can be identified,and zone 3 venules are difficult to find. The formationof nodules is often slow because of an inhibitory effectof alcohol on hepatic regeneration. The amount of fat isvariable and acute alcoholic hepatitis may coexist. Withcontinuing necrosis and replacement by fibrosis, the cirrhosismay progress from a micro - to a macronodularpattern, and this is usually accompanied by a reductioninsteatosis. When this end - stage picture is reached, analcoholaetiology is difficult to confirm on histologicalgrounds. Cirrhosis may follow pericellularfibrosiswithout apparent hepatic necrosis and inflammation.”



“Acute alcoholic hepatitis. Hepatocytesare ballooned and contain micro – andmacrovesicular fat and clumps of purplish – redMallory ’ s alcoholic hyaline. (Chromophobeanilineblue, ×100.)”



“IMAGE:Electron micrograph of liver in a patient with alcoholic liver disease. Note the deposition of collagen fibrils in Disse’ s space (arrowed). This could interfere with oxygen and metabolite exchange between blood and hepatocytes.”

Overall body effects

"Alcohol affects all parts of the body including:

- Blood and immune system
- Bones and muscles
- Brain and nervous system
- Breasts (in women)
- Eyes
- Heart and blood pressure
- Intestines
- Kidneys and fluid balance
- Liver
- Ungs
- Mental health
- Mouth and throat
- Pancreas and digestion of sugar
- Sexual and reproductive system – men
- Sexual and reproductive system – women
- Skin and fat
- Stomach and food pipe (oesophagus)."

“As well as potentially affecting the physical and mental health of individuals in many ways, chronic and heavy alcohol use can increase the risk of death[9] eitherdirectly, for example through acute alcohol poisoning or because alcohol causes a fatal disease such as cancer, or indirectly, such as alcohol being a factor in violent death or suicide. Alcohol contributes to a high burden of disease in society in terms of years that people spend with disability or in poor health because of alcohol-related illnesses or injuries. Unintentional injuries from alcohol use often result from falls, burns, motor vehicle accidents, assaults and drowning.”

Blood and immune system

“Long-term effects of alcohol use: Chronic heavy alcohol use can cause abnormalities in the blood, leading to anaemia (low haemoglobin, the component of blood that carries oxygen around the body) and low platelets (platlets help preven bleeding) and suppresses the immune system (affects WBCs that fight infections), making it more difficult forthe body to fight off both viral and bacterial infections.People who drink heavily over a long time are more likely to suffer from infections after surgery, burns, trauma, hepatitis C infection, HIV/AIDS, meningitis, tuberculosis and pneumonia (acute inflammationof the lung, usually due to infection)”

Bones and muscles

“Immediate effects of alcohol use: Alcohol use causes many different types of injuries, including injuries from road traffic accidents, assaults and falls.This is usually because high levels of blood alcohol impair the brain’s thought processes and the coordination of muscles, causing clumsiness and difficulty walking.Common injuries seen at the emergency department include cuts, bruises, sprains and broken bones.The risk of injury in the six hours after drinking doubles with four standard drinks and increases rapidly the more alcohol is drunk ona single occasion.”

Long-term effects of alcohol use:

“Moderate alcohol use may protect against osteoporosis(thinning of the bones, which makes the bones morelikely to break). However, chronic heavy alcoholuse interferes with the absorption of calcium and bone formation and can actually lead to osteoporosis.Chronic heavy use is also associated with a painful condition where bone tissue dies (osteonecrosis), gout (a type of arthritis or inflammation of the joints, often affecting the joint of the big toe), and musclewasting and weakness.”

Brain and nervous system

“Immediate effects of alcohol use:Being drunk impairs judgment, inhibitions andconcentration, and in increasing amounts leads to drowsiness and coma.The loss of memory for a period of drunkenness (alcoholic blackout) can occur in occasional as well as regular heavy drinkers, and is due to alcohol interfering with the laying down of memories.”

“Long-term effects of alcohol use:Chronic heavy alcohol use can damage the brain and nerves in a variety of ways. Some damage to the brain, from mild to severe, occurs in around half of chronic heavy alcohol drinkers. This may be a result of thiamine (vitamin B1) deficiency (secondary to alcohol use, either because of poor diet or because alcohol reduces the absorption of thiamine from the gut andinterferes with how thiamine is used in the body).”

“Thiamine deficiency can cause an acute, severe, lifethreateningdisorder called Wernicke’s encephalopathy which usually presents with symptoms of abnormalor paralysed eye movements, difficulty walking and confusion. It also causes a chronic condition of memory loss (variously called Korsakoff’s syndrome, psychosis or dementia), where loss of old memories occurs and difficulties in laying”

“down new memories may be profound. Both of these disorders are ultimately fatal without treatment with thiamine. Chronic heavy alcohol use can also damage the part of the brain responsible for balance and coordination (the cerebellum), leading to instability and problems with walking.It can also damage peripheral nerves in the body, leading to pain, weakness, numbness and the inability to sense touch. In rare cases it can damage specific centres in the brain, leading to loss of mental function, inability to walk and death and can lead to the development of epilepsy (chronic fits) and sleep disturbances. Although individuals suffering from insomnia sometimes use alcohol to treat the insomnia, tolerance to the sedating effect of alcohol is likely to occur, increasing the risk of excessive use.The relationship between alcohol use and stroke, where there is a sudden paralysis, loss of sensation or inability to talk because the blood supply to the brainis interrupted, is complex. Alcohol increases the riskof hemorrhagic stroke, where the stroke is caused by bleeding in the brain. However, low to moderate alcohol use (one to two drinks a day) reduces the risk of ischemic stroke, which is caused by blockage of the blood vessels in the brain, but higher levels of alcoholuse increase the risk of ischemic stroke.”

Heart and blood pressure

Long-term effects of alcohol use

“The evidence for the effect of alcohol on the heartis mixed. There is an opinion that light to moderatealcohol use (up to one standard drink per day forwomen and up to two standard drinks per day formen) can, in older age groups, reduce the risk ofdeveloping and dying from coronary artery disease(narrowing and blockage of the arteries supplyingblood to the heart resulting from the build-upof fatty deposits inside the walls of the arteries(atherosclerosis), which can cause angina and heartattacks). This appears to be because small quantitiesof alcohol alter the lipids and clotting factors in theblood to make them protective against heart disease. However, heavy drinking (both chronic and a pattern ofheavy drinking sessions) increases the risk of coronary artery disease. Heavy drinking (chronic and/orat a single session) is also associated with suddendeath from heart failure, with irregular heartbeatsand with chronic disease of the heart muscle (dilatedcardiomyopathy). Dilated cardiomyopathy leads to heart failure, where the heart can no longer pumpblood around the body effectively. Heavy chronic alcohol use is also linked to high blood pressure, particularly in men. Blood pressureincreases with drinking more than two or three drinksa day on average and restriction of alcohol lowers the blood pressure.”

“Drinking alcohol in order to ‘protect the heart’ is notadvisable, since alcohol is an addictive drug that causescancer, increases the risk of”

“injury and causes damage tothe fetus in pregnant women. People can find it difficultto limit their drinking to one or two standard drinks a dayand heavy drinking actually increases the risk of heart disease and.People who have risk factors for orhave established heart disease should focus on otherfactors such as cigarette smoking, high cholesterol,high blood pressure, diabetes, overweight and physicalinactivity. Young and middle-aged adults, especiallywomen, are more likely to experience harm thanbenefit from alcohol use due to risk from injury and,for women, increased risk from breast cancer.”

Kidneys and fluid balance

“Immediate effects of alcohol use: Alcohol is a diuretic, meaning that it causes water to be lost from the body through the kidneys (into urine), which can lead to dehydration. Alcohol can also cause the loss of important minerals and salts fromthe body such as magnesium, calcium, phosphate, sodium and potassium, either directly or because alcohol induces vomiting. Low levels of these elementscan cause many problems ranging from irregular heartbeats to seizures.”

Liver

“Long-term effects of alcohol use:Chronic heavy alcohol use can damage the liver,causing alcoholic liver disease. This occurs acrossa spectrum from fatty liver, to acute alcoholic hepatitis, to cirrhosis.Fatty”

“liver, where fat builds up in the liver cells, is verycommon in heavy drinkers and is reversible if drinkingis reduced. However, a small percentage of people withfatty liver will develop alcoholic hepatitis, cirrhosisor liver cancer.”

“Alcoholic hepatitis develops in 10 to 35 percent ofheavy drinkers and is an acute injury to the liverwhich can present with symptoms of feeling unwell,tiredness, jaundice (yellow skin and whites of eyes),swollen stomach and enlarged, tender liver. Deathfrom liver failure can occur in severe cases.Cirrhosis of the liver develops in 5 to 15 percent ofheavy drinkers and is where the liver is permanentlydamaged and cells are replaced by scar tissue, so theliver can no longer function (to detoxify the body,make vital proteins, store vitamins and sugars,and make chemicals necessary for digestion).Cirrhosis can also lead to death from liver failure.”

“Treatment for alcoholic liver disease must includestopping the drinking of alcohol. Alcohol also causesliver cancer, and treatment options are often limitedif alcoholic liver disease is present or the cancer hasspread widely by the time of diagnosis. This meansliver cancer is often quickly fatal.”

Lungs

“Immediate effects of alcohol use: Being drunk increases the risk of pneumonia(inflammation of the lungs, usually caused by infection from bacteria or viruses).This is because, at high blood concentrations, alcohol is sedating and relaxes the mouth and throat, suppresses reflexes (like the gag and cough reflexes), and reduces the ability of the lungs to clear mucus and foreign matter, so that vomit, saliva or other substances may enter the lungs and cause inflammation and infection (bronchitis or pneumonia).”

“Long-term effects of alcohol use: Chronic heavy alcohol use is also associated withhigher rates of pneumonia, tuberculosis (an infectious disease that affects primarily the lungs but also any other part of the body), and acute respiratory distress syndrome (ARDS – a life-threatening condition in which the lungs fill with fluid, which occurs as a rare complication of pneumonia, trauma and severe infections). In addition to the ways in which acute alcohol use can cause pneumonia, chronic heavy alcohol use also impairs the immune system and changes the bacteria present in the mouth to those more likely to cause infections, making people morevulnerable to pneumonia”.

Mental health

“Immediate effects of alcohol use: Many people use low doses of alcohol for relaxation and to relieve tension, nervousness and”

“stress.However, in some people alcohol creates rather than reduces stress through stimulating stress hormones.Alcohol affects mood in a variety of ways, and can make people feel happy, sad or aggressive, and can also cause moods swing. However, there is a risk of becoming dependent on alcohol if it is used as a primary means to relieve stress and anxiety without addressing the underlying causes. Because it removes inhibitions and increases aggression and recklessness, alcohol is often found in the blood of people who self-harm,or attempt or complete suicide.”

“Long-term effects of alcohol use: Alcohol is addictive and can lead to dependency. This is where the body requires more alcohol to achieve the desired effect (e.g. altered mood), where use of alcohol interferes with a person’s life (causing legal, work/study, relationship or social problems), where a personcontinues to use alcohol despite it causing physical or mental problems, and where, if alcohol is not taken, withdrawal symptoms occur. The severity of withdrawal symptoms depends on the quantity of alcohol consumed and the length of the drinking session. Symptoms include tremors of the hands, which commonly occurs the morning after the drinking session and may be relieved by more alcohol. If alcohol is not taken, symptoms can progress to insomnia, increased heart rate, temperature and blood pressure,”

“sweating, agitation, nausea, flushing of the face, nightmares, hallucinations and seizures.”

“The most serious withdrawal syndrome is ‘delirium tremens’, which develops in about 5 percent of peoplewith alcohol withdrawal and by definition includes the symptom of delirium (an altered and confused state of mind).This syndrome has a death rate of around 5 percent.”

“In people who drink heavily, alcohol commonly causes mood disorders, including depression, anxiety and psychosis (a mental illness defined by changes inpersonality, a distorted sense of reality, and delusions).If these disorders only occur during drinking sessions or withdrawal, they will usually resolve once drinking is stopped. Alcohol abuse and dependency are also common in people with pre-existing mental health conditions.”

LIVER PARAMETERS

“Liver function tests (LFTs) or liver biochemical tests can be used to screen for liver disease, direct diagnostic work - up, and assess severity, prognosis and response to treatment. Although the term LFT is firmly entrenched in the medical literature, this term is frankly erroneous as these investigations provide indirect” evidence “of hepatobiliary disease. LFTs that more” accurately “reflect liver function are serum albumin, serum bilirubin and prothrombin time, which is standardizedto”

“the international normalized ratio (INR). As the” prevalence “of liver disease is only between 2 and 4% in the general population (higher for fatty liver disease” andviral “hepatitis), the more investigations are multiplied, the greater chance there is of a biochemical abnormality being demonstrated. A few simple tests of established value should be used and if an abnormality is found itshould be repeated to confirm it is real.”

“LFT abnormalities may be classified into the” following “categories:”

“Hepatocellular (elevations predominantly in aspartate aminotransferase (AST) and alanine” aminotransferase “(ALT)); cholestatic (increases” predominantly “in alkaline phosphatase (ALP), γ – glutamyltranspeptidase(γ - GT) and bilirubin); and infiltrative(increases in ALP, γ - GT and occasionally bilirubin).The tests most useful in the diagnostic work - up of” jaundice “are the ALP, aminotransferase and bilirubin tests. An isolated rise in serum unconjugated bilirubin suggests Gilbert’s syndrome, haemolysis”, ineffective “erythropoiesis or use of medications such” asbunamiodyl (“cholecystographic agent) flavaspidic acid, probenicid and rifampicin.”

“The severity of liver cell damage is assessed by serial measurement of total bilirubin, albumin and” prothrombin “time after vitamin K. This is reflected by theirincorporation into the Childs – Pugh (CP) score and Model for Endstage Liver Disease (MELD), which are used to estimate severity and prognosis of liver disease and assess

candidacy for liver transplantation", respectively."Rising arterial ammonia levels also reflect severe hepatic dysfunction in" patients with acute liverfailure (ALF) whereas hyperammonaemia in decompensated "cirrhosis does not always correlate with hepatic encephalopathy or progression of liver disease."

"The diagnosis of minimal hepatocellular damage may be suspected by noting minimally elevated" aminotransferases "and sometimes serum bilirubin. Patients who are heavy drinkers of alcohol with or without liver disease (ALD) may have just a raised γ - GT with or without biochemical evidence of liver damage.However, this degree of biochemical abnormality also occurs in well - compensated cirrhosis, heart failure and fever, reflecting the lack of sensitivity and specificity of these investigations for diagnosing and assessing" severity "of liver disease."

Bile pigments

"Bilirubin: "Total bilirubin is increased in cholestatic and" hepatocellular "liver disease more commonly than infiltrative disease. It is often associated with a rise in liver enzymes.Bilirubin is predominantly conjugated and water soluble. Patients with marked hyperbilirubinaemia (bilirubin > 425 μ mol/L) often have severe liver disease coexisiting with renal dysfunction or another cause of unconjugated hyperbilirubinaemia, such as haemolysis. An isolated rise in bilirubin without enzyme"

elevation “should fi rst “be fractionated to determine if the” aetiology “is familial or due to haemolysis.”

“Serum bilirubin estimations are based on the van den Bergh diazo reaction, which involves the” spectrophotometric “detection of azo derivatives derived by the” reaction “of plasma with the diazonium ion of sulphanilicacid . This reaction separates bilirubin into a water - soluble direct form representing conjugated bilirubin and an indirect, lipid - soluble form representing” unconjugated “bilirubin. These diazo reactions are subject to error, particularly at low total serum bilirubin” concentrations.”More accurate methods for estimation include alkaline methanolysis with chloroform extraction, high performance gas liquid chromatography (HPGLC), thin layer chromatography (TLC) and spectrophotometric determination, but are too elaborate to be clinicallyuseful”

“Faecal inspections are an important investigation in jaundice. Clay - coloured stools indicate cholestatic” jaundice “but may also occur in hepatocellular jaundice. The colour will be normal in haemolytic jaundice. Rarely, pale stools occur in very severe bilirubin glucuronyltransferase deficiency. Bilirubin cannot be detected in the *urine* of normal subjects as bilirubin is predominantly unconjugated, insoluble in water and bound to albumin. In contrast, bilirubin glucuronides, the products of bilirubin” conjugation,”are water soluble.

They appear in the urine even when serum total bilirubin is normal as the renal" threshold "for glomerular filtration of conjugated bilirubin is low. Conjugated bilirubin, however, will bind covalently to albumin when jaundice is prolonged and severe, giving rise to a complex called δ bilirubin (or" bilioprotein) ".δ bilirubin has a long half - life, cannot be renallycleared and accounts for the absence of bilirubinuria and slow resolution of jaundice in patients recovering from severe hepatobiliary disease".

"Urobilinogen

Bacterial β - glucuronidases convert bilirubin in the colon to a series of colourless tetrapyrroles collectively called urobilinogen of which 80 – 90% is normally excreted in the faeces either unchanged or as oxidized orange" derivatives "called urobilins. The remaining 10 – 20% is absorbed and undergoes an enteric circulation with re-excretion into bile by the liver while a small proportion is excreted in the urine. This complex process depends on several factors such as urine flow rate and pH.Spot urinary urobilinogen is a poor predictor of hepatic disease with a high proportion of false – negative results"

Serum enzyme tests

These tests usually indicate the type of liver injury, whether hepatocellular, cholestatic or infiltrative but cannot differentiate one form

of hepatitis from another or determine whether cholestasis is intra - or extrahepatic.They are valuable in directing specific serological tests, imaging or liver biopsy to reach the diagnosis. Only a few tests are necessary and the combination of “normal ALT values should be adjusted for body mass index and sex . During pregnancy, ALT, AST and γ - GT levels, as well as bile acid and bilirubin concentrations remain within the normal range, whereas an elevated alkaline phosphatase is of placental origin during the third trimester.”

“Aminotransferases

The aminotransferases (previously called aminotransaminases) catalyse transfer of amino groups from either aspartate or alanine to the keto group of α –ketoglutaricacid forming oxaloacetic acid (OAA) and pyruvic acid, respectively. These enzymes are important in gluconeogenesis as they catalyse glucose synthesis fromnon - carbohydrate sources. Enzymatic reduction of oxaloacetic acid and pyruvic acid to malate and lactate, respectively, is coupled with oxidation of the reducedform of nicotinamide dinucleotide (NADH) to nicotinamide dinucleotide (NAD). As only NADH absorbs light at 340 nm, this reaction can be followed spectrophotometrically to accurately assay these enzymes.”

"Aspartate aminotransferase (AST; serum glutamic oxaloacetic transaminase or SGOT) is an isoenzyme located in the cytoplasm and mitochondria of manytissues. Although normal AST serum activity is" "cytosolic in origin, 80% of AST activity within the liver is mitochondrial and predominates in periportal hepatocytes."

"In decreasing order of concentration AST is present in large quantities in liver, heart, skeletal muscle, kidneys, brain, pancreas, lungs, leucocytes and erythrocytes.Macro - AST is a rare condition characterized by isolated AST elevation due to binding of AST with an immunoglobulin which is not cleared by the blood or kidneys] . It is a benign condition and is not reflective of liver disease. Markedly low AST levels have been reported in patients on chronic haemodialysis, possibly due to dialysis or pyridoxine deficiency."

"Alanine aminotransferase (ALT; serum glutamic pyruvic transaminase or SGPT) is a cytosolic enzyme also present in liver. Although the absolute amount is less than AST, a greater proportion is present in liver compared with kidney, heart and skeletal muscles. A serum increase is therefore more specific for liver damage than AST".

"Transferase determinations with viral serologies are useful in the early diagnosis of viral hepatitis, but there is no correlation between transferase level with eitherthe degree of hepatocyte necrosis or prognosis.Measurements should be performed promptly as these enzymes

“have short half - lives (AST 12 – 22 h; ALT 37 – 47h) . Patients may develop fatal acute hepatic necrosis despite falling transaminase values”.

“Routine screening may show unexpectedly raised aminotransferase levels. These are often due to non - alcoholic fatty liver disease (NAFLD), alcohol abuse, viral hepatitis and haemochromatosis. Less common causes include autoimmune hepatitis, α1-antitrypsin deficiency, Wilson’s disease, drug – induced liver disease and non - hepatic disorders such as Addison ’ s disease, anorexia nervosa, celiac disease and hyperthyroidism. Important causes of markedly elevated transaminases are viral hepatitis (including herpes simplex hepatitis), paracetamol(acetaminophen) or other drug - induced hepatotoxicity, ischaemic hepatitis and severe autoimmune hepatitis .Calculous biliary obstruction with cholangitis is animportant but frequently under appreciated cause of AST elevation greater than 10 times the upper limit of normal, which may improve with antibiotics over 48 –72 h despite unresolved obstruction. Very high levels are unusual in ALD and suggest a coexisting disorder such as paracetamol toxicity or acute viral hepatitis. A ratio of AST to ALT greater than two may be useful in diagnosing ALD. This occurs because damage is primarily mitochondrial (thus more AST is released systemically) and ALT synthesis is more sensitive than AST to pyridoxal 5 - phosphate deficiency,leading to lower serum ALT levels . An elevated ASTTo ALT ratio has also been described as”a

“specific but non - sensitive marker of advanced fibrosis or cirrhosis in NAFLD and chronic hepatitis C”.

“Alkaline phosphatise”

“The alkaline phosphatases (ALP) are a group of enzymes that catalyse hydrolysis of phosphate esters at neutral pH. Magnesium and zinc are important co - factors. ALP in the liver is cytosolic, associated with sinusoidal and canalicular membranes and rises in cholestasis and to a lesser extent when liver cells are damaged.”

“ALP is present, in decreasing order of quantity, in placenta, ileal mucosa, kidney, bone and liver but more than 80% of serum ALP is from the liver or bone. ALP half - life is 3 days. Bone, liver and kidney ALP are coded by the same gene and share a common protein structure but differ in their carbohydrate content. Mechanisms of the increase are believed to be related to increased hepatobiliary synthesis from enhanced translation of messenger ribonucleic acid of ALP and serum secretion through canalicular leakage into the sinusoid rather than failure to excrete ALP. Due to *de novo* ALP synthesis in acute biliary obstruction, serum levels are initially normal in contrast to marked transferase elevations. Serum hepatic ALP may be distinguished from bone ALP by isoenzyme fractionation but this is not routinely carried out as a concomitant rise in γ - GT confirms ahepatobiliarysource.An isolated rise in ALP may also be”

“of intestinal origin, as observed in patients with blood groups O and B who secrete intestinal ALP postprandially. As these enzymes may” “remain elevated for up to 12 h, levels mustbe determined under fasting conditions . Up to 52% of patients with mild isolated ALP elevations (less than two fold elevation) will have enzyme normalizationwithin 1 – 3 months although in hospitalized patients, sepsis in the absence of jaundice may account for up to 32% of cases. Raised ALP levels are sometimes observed with primary or secondary hepatic tumours, even without jaundice or involvement of bone. Increased values without jaundice are also found with other space -occupying lesions or infiltrative disease such as amyloid, abscess, lymphoma or granulomas. Non - specific mild elevations are seen in a variety of conditions including Hodgkin ’ s disease, heart failure, hyperthyroidismand up to 15% of patients with renal cell carcinoma in the absence of involvement of the hepatobiliary system or bone (Stauffer ’ s syndrome). Low ALP levelsare associated with hypothyroidism, Wilson’s disease with haemolysis, congenital hypophosphatasia, pernicious anaemia, zinc deficiency, severe hepatic insufficiency and in children recovering from severe enteritis.”

“Gamma” glutamyltranspeptidase or transferase

“Gamma glutamyltranspeptidase (γ - GT) is a membrane-bound enzyme that catalyses transfer of γ glutamyl groups of peptides such as”

“glutathione to other amino acids. Levels are increased in cholestasis and hepatocellular disease and occur in the same spectrum of hepatobiliary” “diseases as elevated ALP. γ - GT is ubiquitous but in decreasing order of abundance is present in proximal renal tubule, liver, pancreas (acinar cells and ductules) and intestine. Serum γ - GT activity arises primarily from the liver and, within the hepatobiliary system, is present in highest concentration in the epithelium lining of fine biliary ducts. The main role of this test is to confirm a raised ALP is of hepatobiliary origin”.

“An isolated rise in γ - GT is seen in patients with alcohol abuse, even without liver disease, due to microsomal enzyme induction and impaired clearance (half - life of 7 – 10 days increases to 28 days). Screening for γ - GT may have led to more alcohol abusers being identified although levels do not rise in one - third of individuals. There also is no correlation between alcohol consumption and elevated serum γ - GT levels with hepatic γ – GT in patients with biopsy - proven alcoholic liver disease. An increased level can lead to over - investigation inan individual who has never taken alcohol or a socialdrinker who has never abused alcohol.”

The Hematological Complications of Alcoholism

“Alcohol Effects On The Bone Marrow And On RBC Production :Alcohol is the most commonly used drug whose consequences include”

“thesuppression of blood cell production, or hematopoiesis. Because its toxiceffects are dose dependent, however, significantly impaired hematopoiesisusually occurs only in people with severe alcoholism, who also may sufferfrom nutritional deficiencies of folic acid and other vitamins that play a rolein blood cell development. Chronic excessive alcohol ingestion reduces thenumber of blood cell precursors in the bone marrow and causes characteristicstructural abnormalities in these cells, resulting in fewer-than-normal or non-functional mature blood cells. As a result, alcoholics may suffer frommoderate anemia, characterized by enlarged, structurally abnormal RBC’s;mildly reduced numbers of WBC’s, especially of neutrophils; and moderatelyto severely reduced numbers of platelets. Although this generalizedreduction in blood cell numbers (i.e., pancytopenia) usually is not progressiveor fatal and is reversible with abstinence, complex aberrations ofhematopoiesis can develop over time that may cause death.”

“Many bone marrow abnormalities occurring in severe alcoholics affectthe RBC precursor cells. These abnormalities most prominently includeprecursors containing fluid-filled cavities (i.e., vacuoles) or characteristiciron deposits.”

Development of Vacuoles in RBC Precursors

“The most striking indication of alcohol’s toxic effects on bone marrowcells is the appearance of numerous large vacuoles in early RBC precursorcells. It is unknown whether these vacuoles affect the cell’s function andthus the drinker’s health; however, their appearance generally is consideredan indicator of excessive alcohol consumption.3 The vacuoles usuallyappear in the pronormoblasts 5 to 7 days following the initiation of heavyalcohol consumption. Moreover, the vacuoles on average disappear after 3to 7 days of abstinence, although in some patients they persist for up to 2 weeks. To a lesser extent, vacuoles also develop in the granulocyte precursors of alcoholics. This finding is not specifically alcohol related, however, because other events that interfere with WBC production (e.g., infections) may induce similar structural changes in the granulocyte precursors. The precise mechanism underlying vacuole development in blood cell precursors currently is unknown. Microscopic analyses of early blood cell precursors grown in tissue culture suggest that when the cells are exposed to a wide range of alcohol concentrations, the membrane surrounding each cell is damaged. These alterations in membrane structure may play an influential role in vacuole formation”.

ALCOHOL’S EFFECTS ON IRON METABOLISM

“In addition to interfering with the proper absorption of iron into the hemoglobin molecules of red blood cells (RBC’s), alcohol use can lead to either iron deficiency or excessively high levels of iron in the body.Because iron is essential to RBC functioning, iron deficiency, which is commonly caused by excessive blood loss, can result in anemia. In many alcoholic patients, blood loss and subsequent iron deficiency are caused by gastrointestinal bleeding. Iron deficiency in alcoholics often is difficult to diagnose, however, because it may be masked by symptoms ofother nutritional deficiencies (e.g., folic acid deficiency) or by coexisting liver disease and other alcohol-related inflammatory conditions. For an accurate diagnosis, the physician must therefore exclude folic acid deficiency and evaluate the patient’s iron stores in the bone marrow. Conversely, alcohol abuse can increase iron levels in the body. For example, iron absorption from the food in the gastrointestinal tract may be elevated in alcoholics. Iron levels also can rise from excessive ingestion of iron-containing alcoholic beverages, such as red wine. “

“Theincreased iron levels can cause hemochromatosis, a condition characterized by the formation of iron deposits throughout the body (e.g., in the liver, pancreas, heart, joints, and gonads). Moreover, patients whose chronic alcohol consumption and hemochromatosis have led to liver cirrhosis are at increased risk for liver cancer.”

SideroblasticAnemia

"One component of RBC's is hemoglobin, an iron-containing substancethat is essential for oxygen transport. Sometimes, however, the iron is notincorporated properly into the haemoglobin molecules. Instead, it is convertedinto a storage form called ferritin, which can accumulate in RBC precursors, often forming granules that encircle the cell's nucleus. These ferritin- containing cells, which are called ringed sideroblasts, cannot mature further into functional RBC's. As a result, the number of RBC's in the blood declines and patients develop anemia. Many patients also have some circulating RBC's that contain ferritin granules called Pappenheimer bodies. The presence of these cells in the blood serves as an indicator of sideroblasticanemia and can prompt the physician to perform a bone marrow examination to confirm the diagnosis.Sideroblasticanemia is a common complication in severe alcoholics: Approximately one-third of these patients contain ringed sideroblasts in their bone marrow. Alcohol may cause sideroblasticanemia by interfering with the activity of an enzyme that mediates a critical step in haemoglobin synthesis. Abstinence can reverse this effect: The ringed sideroblasts generally disappear from the bone marrow within 5 to 10 days, and RBC production resumes. In fact,

excess numbers of young RBC's called reticulocytes can accumulate temporarily in the blood, indicating higher-than normal RBC production."

MegaloblasticAnemia

"Blood cell precursors require folic acid and other B vitamins for their continued production. Under conditions of folic acid deficiency, precursor cells cannot divide properly and large immature and non-functional cells (i.e., megaloblasts) accumulate in the bone marrow as well as in the bloodstream. This impaired hematopoiesis affects mainly RBC's, but also WBC's and platelets. The resulting deficiency in RBC's, WBC's, and platelets (i.e., pancytopenia) has numerous adverse consequences for the patient, including weakness and pallor from anemia, infections resulting from reduced neutrophil numbers, and bleeding as a result of the lack of platelets. Megaloblasts occur frequently in the bone marrow of alcoholics; they are particularly common among alcoholics with symptoms of anemia, affecting up to one-third of these patients. These alcoholics generallyalso have reduced folic acid levels in their RBC's. The most common causeof this deficiency is a diet poor in folic acid, a frequent complication inalcoholics, who often have poor nutritional habits. In addition, alcoholingestion itself may accelerate the development of folic acid deficiency by altering the absorption of folic acid from food."

ALCOHOL-RELATED RBC DISORDERS

"Alcohol-related abnormalities in RBC production manifest themselves not only in the bone marrow but also through the presence of defective RBC's in the blood. For example, grossly enlarged RBC's can occur in the blood—a condition called macrocytosis— as well as oddly shaped RBC's that are subject to premature or accelerated destruction (i.e., hemolysis) because of their structural abnormalities. As a result, alcoholics frequently are diagnosed with anemia."

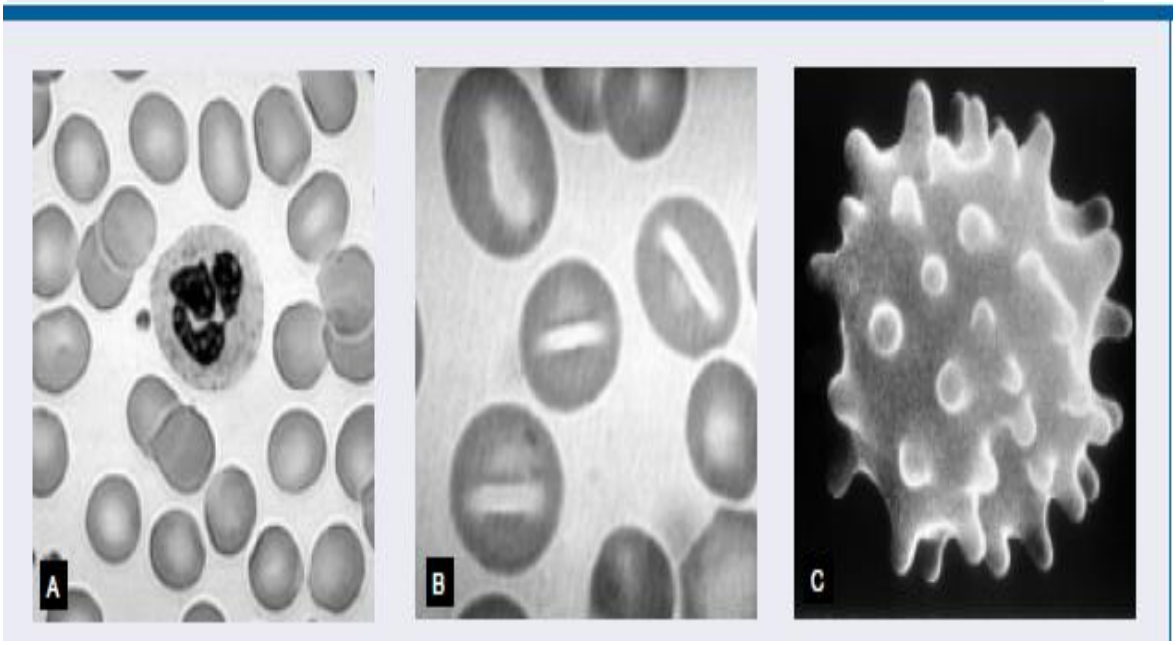
Macrocytosis

"The routine examination of blood samples from alcoholic and non-alcoholic patients using automated blood cell counters has resulted in the identification of many people in whom the average size of individual RBC's—The mean corpuscular volume (MCV)—is significantly larger than normal. However, an increased MCV does not automatically lead to a diagnosis of macrocytosis. For example, cells with an increased MCV can be found in patients with folic acid or vitamin B12 deficiency (as in the case of megaloblasticanemia) or with chronic liver disease. Moreover, the presence of enlarged RBC's in the blood can be indicative of a variety of disorders in addition to alcoholism, including different kinds of anemia and a dysfunction of the thyroid gland. To establish a diagnosis of"

“macrocytosis, the physician must examine the blood cells under a microscope to identify structural features characteristic for each disorder. Thus, the enlarged RBC’s in patients with macrocytosis generally are uniformly round, in contrast to the more oval cells characteristic of megaloblasticanemia. In addition, a diagnosis of macrocytosis resulting from alcohol requires that the physician investigate all potential causes of RBC enlargement, including the patient’s alcohol-consumption history.”

Alcohol Induced Structural Abnormalities in RBC’s”

Alcohol-induced structural abnormalities in red blood cell (RBC) structure. (A) Normal RBC's have a characteristic disclike shape; the cell in the center is a neutrophil. (B) Stomatocytes have a defect in their membranes that causes them to assume a mouth-, or stoma-, like shape when viewed under a microscope. (C) Spur cells are characterized by spikelike protrusions that result from the assimilation of excess cholesterol into the cell's membrane.



Evaluation of Macrocytosis

“”The causes of macrocytosis can be broadly classified as megaloblastic and nonmegaloblastic. Megaloblastic” processes

“characterized on the peripheral smear by macro-ovalocytes and hypersegmented neutrophils, which are absent in nonmegaloblastic macrocytic processes. Nonmegaloblastic processes have round macrocytes or macroreticulocytes.Because the mechanisms producing macrocytosis are not completely understood, the separation between megaloblastic and nonmegaloblastic causes is somewhat artificial. However, this concept remains useful for identifying the most predominant etiology for macrocytosis. For example, whereas the effect of alcohol is thought to be primarily a nonmegaloblastic process, in chronic alcoholism there may be concomitant vitamin B12 or folate deficiency. In megaloblastic processes, erythrogenic precursors are larger than mature red blood cells (RBCs) because folate and vitamin B12 deficiencies result in defective RNA and DNA syntheses. Serum elevations in homocysteine and methylmalonic acid result from defective biochemical processes in folate and B12 deficiencies, and could be used to clarify the cause of megaloblasticanemia, although this is not yet standard clinical practice. Nonmegaloblastic processes develop from multiple mechanisms and have not been fully outlined. Macrocytosis can occur when there is increased RBC production secondary to peripheral blood cell destruction (i.e., hemolysis) or loss (i.e., hemorrhage), leading to a reticulocytosis. Reticulocytes are incompletely processed RBCs and, therefore, are slightly larger than the average RBC.”

Megaloblastic (involving vitamin B_{12} and/or folate deficiencies)
Atrophic gastritis
Enteral malabsorption
Human immunodeficiency virus treatments
Anticonvulsants (some cause folate depletion)
Primary bone marrow disorders
Nitrous oxide abuse
Inherited disorders
Nonmegaloblastic
Alcohol abuse
Medication side effects (see Table 3)
Myelodysplasia
Hypothyroidism
Liver disease
Hemolysis
Hemorrhage
Chronic obstructive pulmonary disease
Splenectomy
False elevations
Cold agglutinins
Hyperglycemia
Marked leukocytosis

NOTE: *Diagnoses listed from most to least common.*

Differential Diagnosis of Macrocytosis

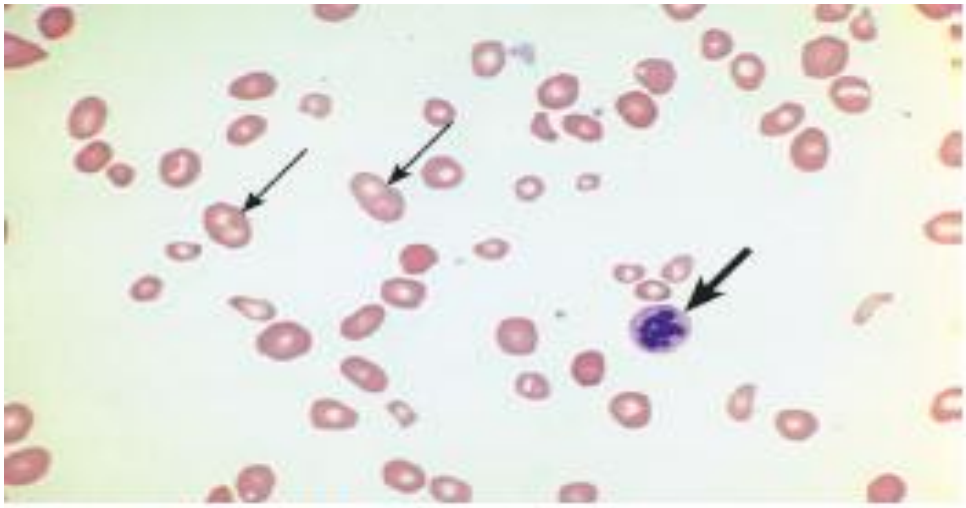


Figure 1. Megaloblastic anemia, with macro-ovalocytes *(thin arrows)* and hypersegmented neutrophils *(thick arrow)*.

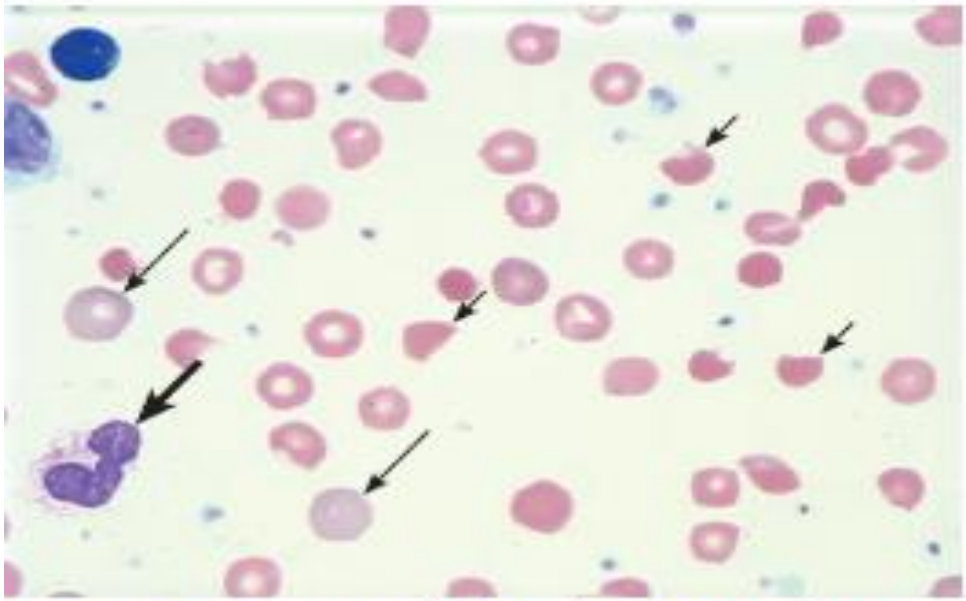


Figure 2. Microangiopathic hemolytic anemia (nonmegaloblastic), with polychromatophilic macrocytes *(thin arrows)* and normally segmented neutrophils *(thick arrow)*. Schistocytes *(short arrows)* typical of this particular disorder are also present.

Diagnostic Strategy

"Once macrocytosis is identified, the history and physical examination help narrow the differential diagnosis. The presence of anemia, the degree of elevation of he mean corpuscular volume, and the patient's overall health guide how aggressively the work-up progresses. At least some amount of investigation is warranted if the diagnosis is not readily apparent or if the patient is anemic (defined by the World Health Organization as a haemoglobin level less than 13 g per dL [130 g per L] in men and less than 12 g per dL [120 g per L] in women). Physicians should begin by ordering a peripheral smear, a reticulocyte count, and a vitamin B12 serum level for all patients with macrocytosis. It may be necessary to specifically order a reticulocyte index in some laboratories, which assesses if there is an adequate bone marrow response. Hemorrhage or hemolysis is the most likely cause if the reticulocyte count is elevated, but anemia recovery also causes an elevation in the reticulocyte count. Measures of vitamin B12 are a useful part of the initial work-up, because if vitamin B12 deficiency is present but undiagnosed, folate repletion will correct the megaloblasticanemia, but not the possible neuropathic changes that occur with B12 deficiency. Although uncommon, consider the possibility of spurious macrocytosis. This may be caused by cold agglutinins, hyperglycemia, or leukocytosis. Cold agglutinins cause the RBCs to clump, making them appear larger to the"

“automatic counter. Hyperglycemic blood is more concentrated, and when it is diluted to measure the mean corpuscular volume, the cells swell more than usual, causing a false elevation.Increased turbidity of a sample with marked leukocytosis also can cause the machine to overestimate the cell size. When the history and physical examination, peripheral smear, B12 level, and reticulocyte count have not lead to an obvious diagnosis, consider a comprehensive metabolic panel to look for liver and kidney disease, thyroid-stimulating hormone for thyroid disorders, and methylmalonic acid and homocysteine levels to assess for vitamin B12 deficiency, despite a normal vitamin B12 level. If the cause remains elusive, consider again whether the degree of anemia or the patient’s overall health warrants referral to a hematologist for bone marrow biopsy, or search for rarer causes, keeping in mind that the most extensive work-up will result in a diagnosis in approximately 90 percent of patients.”

Specific Causes of Macrocytosis

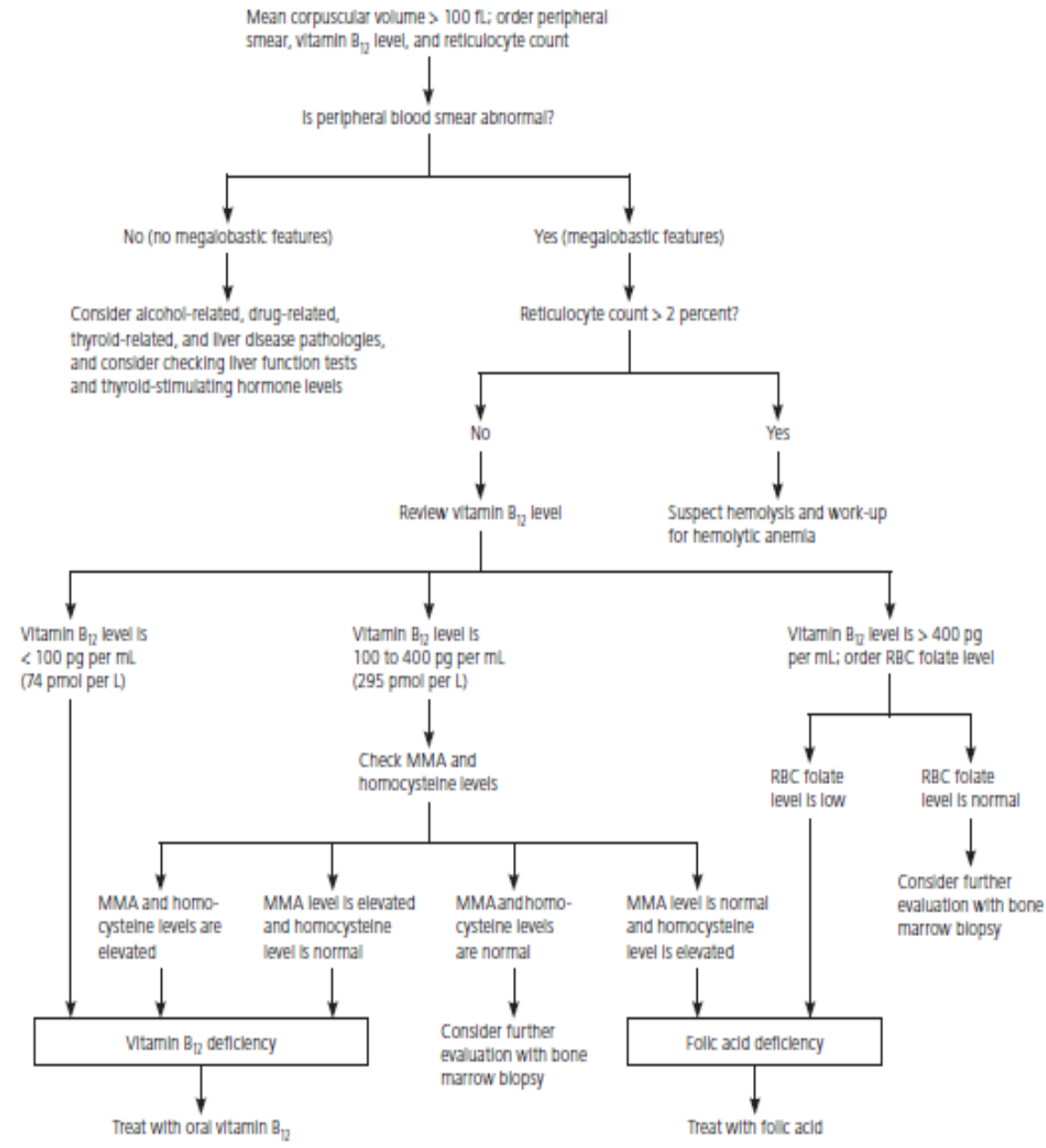
Vitamin B12 Deficiency

“Vitamin B12 is absorbed by the ileum when it is bound by intrinsic factor, which is produced by the parietal cells of the gastric mucosa. In pernicious anemia, the loss of parietal cells leads to insufficient absorption of vitamin B12, which then leads to vitamin B12”

“deficiency over time. Pernicious anemia is most commonly caused by autoimmune atrophic gastritis, in which autoantibodies are directed against parietal cells and intrinsic factor. Less commonly, pernicious anemia can be caused by nonautoimmune gastritis secondary to *H. pylori* infections and Zollinger-Ellison syndrome. Patients with vitamin B12 deficiency may describe paresthesias related to peripheral neuropathy, poor or strict vegan diet, lack of socioeconomic resources, bowel-related symptoms (including diarrhea), or a history of bowel surgery for weight loss. Findings on physical examination may include neurologic signs such as ataxia, decreased proprioception, and vibratory sensation. Patients may also have poor dentition or nonspecific oral stomatitis or glossitis.Because pregnant women take folic acid routinely in prenatal vitamins, macrocytic anemia is much less common during pregnancy. Consider nitrous oxide abuse in at-risk populations, because nitrous oxide inactivates vitamin B12 through oxidation. Other uncommon causes include *Diphyllobothriumlatum*(i.e., fishtapeworm) infection or inherited disorders of cobalamin metabolism, including Imerslund syndrome (a congenital vitamin B12 malabsorption associated with proteinuria). Only 10 percent of persons with vitamin B12 deficiency are actually anemic. The normal range for serum measures of vitamin B12 varies among laboratories. If the vitamin B12 level is borderline low (i.e., 100 to 400 pg per mL [74 to 295 pmol per L]), methylmalonic acid and homocysteine”

"levels should be ordered and, if elevated, may provide evidence of B12 deficiency. The Schilling test (i.e., measuring enteral absorption of vitamin B12) is not widely available at this time."

Macrocytosis
Evaluation of Macrocytic Anemia



“Oral therapy appears to be as effective as intramuscular therapy for the treatment of vitamin B12 deficiency.Relapse of pernicious anemia occurs at a mean intervalImportant for patients to adhere to long-term therapy because the deficiency will recur if treatment is stopped, unless a reversible cause is identified.”

Folate Deficiency

“The history of folate deficiency may mimic the history of vitamin B12 deficiency in regard to poor nutritional intake or absorption. In addition, 35 percent of patients with alcoholism and macrocytic anemia are folate-deficient, which can be caused by poor nutritional intake, malabsorption, hepatobiliary dysfunction, and possibly increased folate catabolism.Some medications that are used to treat seizure disorders, cancer, and autoimmune diseases can lead to folate deficiency. For example, methotrexate directly inhibits dihydrofolatereductase, which leads to a functional folate deficiency. Other medications that affect folate metabolism include 5-fluorouracil (Adrucil), hydroxyurea (Hydrea), pyrimethamine (Daraprim), trimethoprim/sulfamethoxazole (Bactrim, Septra), pentamidine (Pentam), and phenytoin (Dilantin). Medications can also affect folate absorption, including metformin (Glucophage) and cholestyramine (Questran). Supplementing with folate may be necessary when treating a patient with such medications. Serum”

“folate levels are not useful because they fluctuate rapidly with dietary intake and are not cost effective. RBC folate levels more accurately correlate with folate stores and should be performed if folate deficiency is suspected. In differentiating the cause of megaloblastic anemia, a methylmalonic acid level that is within normal range also points toward a diagnosis of folate deficiency,especially if the serum vitamin B12 level is within the normal range. Note that homocysteine levels will be elevated with vitamin B12 and folate deficiencies.”

Alcohol Abuse

“The Michigan Alcoholism Screening test and obtaining γ-glutamyltransferase levels were found to be the two most sensitive tests for detecting alcohol abuse in patients with macrocytosis.Physical findings consistent with alcoholism include gynecomastia, caput medusae, and jaundice. Alcohol use more commonly causes macrocytosis through its toxic effect than through folate deficiency secondary to alcoholism. The mean corpuscular volume is generally less than 110 fL with chronic alcohol use. Abstinence from alcohol rapidly corrects the elevated mean corpuscular volume.”

Bone Marrow Dysfunction

“As noted above, myeloproliferative disorders (sometimes called refractory anemia) are a more common cause of macrocytosis and”

“anemia among older persons than in younger populations. Although the peripheral smear may be suggestive, bone marrow biopsy is required to establish this diagnosis. Referral will likely be necessary for the work-up and management.”

Medications Causing Macrocytosis

Treatments for human immunodeficiency virus: reverse transcriptase inhibitors (e.g., stavudine [Zerit], lamivudine [Epivir], zidovudine [Retrovir])
Anticonvulsants (e.g., valproic acid [Depakote], phenytoin [Dilantin])
Folate antagonists (e.g., methotrexate)
Chemotherapeutics (e.g., alkylating agents, pyrimidine, purine inhibitors)
Trimethoprim/sulfamethoxazole (Bactrim, Septra)
Biguanides (e.g., metformin [Glucophage]), cholestyramine (Questran)

Hemolytic Anemia

“Hemolysis can be an underlying cause of anemia, and several types of hemolytic anemia may be caused by chronic heavy alcohol consumption. Two of these disorders are characterized bythe presence of malformed RBC’s—stomatocytes and spur cells—whereas one alcohol-related hemolytic anemia is caused by reduced phosphate levels in the blood (i.e., hypophosphatemia).Diagnosing hemolysis” in

“alcoholicpatients is not easy, because these patients frequently exhibit confounding conditions, such as alcohol withdrawal, abnormal folic acid levels, bleeding, or an enlarged spleen.”

“Stomatocyte Hemolysis. Stomatocytes are RBC’s with a defect in their membranes that causes the cells to assume a mouth-, or stoma-, like shape when examined under a microscope. Stomatocytes have a shortened life span because they become trapped in the small capillaries of the spleen and are subsequently destroyed. In healthy people, stomatocytes account for less than 5 percent of the RBC’s, whereas their number can be significantly higher in alcoholics. In fact, more than 25 percent of alcoholics exhibit an increased proportion of stomatocytes in the blood (i.e., stomatocytosis).”

“Spur-Cell Hemolysis. Spur cells are distorted RBC’s that are characterized by spike-like protrusions of their cell membrane. These spurs are caused by the incorporation of excess amounts of cholesterol into the cell membrane, resulting in an increase of the cell’s surface area without a corresponding increase in cell volume. Modestly elevated membrane cholesterol levels result in a flattened RBC shape, whereas larger increments of cholesterol cause the membrane to be thrown up into spikes. Spur cells may be prematurely eliminated in the spleen.”

ALCOHOL'S EFFECT ON WBC'S

"Since the 1920's, clinicians have noted an association between excessive alcohol ingestion and the development of infections. These observations suggest that alcohol interferes with the normal production and/or function of WBC's, which form the body's defense against microorganisms and other foreign substances. Because alcoholics commonly develop bacterial infections,much research has focused on alcohol's effects on neutrophils, the primary cell of defense against bacterial invasion. However, alcohol also impairs the function of monocytes and macrophages, which attack bacteria and other microorganisms, and of lymphocytes, which mediate the immune response."

"Neutrophils When a severe bacterial infectionoccurs, the body's response usuallyincludes an increase in the number ofWBC's—especially neutrophils—inthe blood, a condition called leukocytosis.In contrast, alcoholics sufferingfrom bacterial infections often exhibita reduced number of neutrophils in theblood (i.e., neutropenia). For example,in a study of 10 alcoholics with severebacterial pneumonia or other bacterialinfections, neutropenia was present in5 patients when they were admitted tothe hospital and developed in the other5 patients within 24 to 48 hours (Mc-Farland and Libre 1963). The neutropeniawas transient, however, and inseveral patients a rebound leukocytosisoccurred between"

“5 and 10 days afterhospital admission.The observed neutropenia may berelated to impaired neutrophil developmentin the bone marrow. Thus, bone marrow analysis of alcoholicpatients during the neutropenic stagedemonstrated that virtually none ofthe neutrophil precursors had maturedbeyond an early developmental stage.Moreover, the neutrophil stores thatare maintained in the bone marrow toallow a quick response to a bacterialinfection were depleted more rapidlyin active alcoholics than in healthycontrol subjects.Alcohol consumption also interfereswith the neutrophils’ ability toreach the site of an infection or inflammation(i.e., neutrophil delivery).When traveling to such a site, the neutrophilsadhere to the walls of theblood vessels before migrating out ofthe blood vessels into the affectedtissue. In tissue-culture experimentsusing nylon fibers to mimic this adherence,neutrophils could not adhere tothe fibers if the blood samples wereincubated with alcohol. “

“This effectwas more pronounced the higher thealcohol doses were. Neutrophils obtainedfrom intoxicated volunteers hadthe same defect. The degree and durationof this adherence defect correlatedwith the inhibition of neutrophil deliveryobserved in the body. Moreover,drugs that corrected the adherencedefect in tissue-culture experimentsalso improved neutrophil delivery inhumans.The function of neutrophils, includingtheir adhesion ability, is regulatedbyhormonelike substances calledleukotrienes. Thus, the impaired neutrophilfunctioning observed”

“afteralcohol treatment could be attributableto reduced leukotriene production or tothe neutrophils’ inability to respond tothe leukotrienes. Some research resultsindicate that alcohol can interfere withleukotriene production.In an effort to overcome or preventthe alcohol-induced impairment of the body’s antibacterial defense, researchershave studied the effects of a growth factor called granulocyte-colony stimulatingfactor (G-CSF) in animal experiments. During normal neutrophil production in the bone marrow, G-CSF promotes the multiplication and functional activity of neutrophils. The studies found that G-CSF stimulated neutrophil recruitment specifically to the site of an infection and ameliorated the alcohol-induced impairment in the defense against bacterial infections.”

Monocytes and Macrophages

“The monocyte-macrophage system, like neutrophils, constitutes an important line of defense against infections. Monocytes and macrophages clearinvading microorganisms as well as foreign or defective proteins from the blood by engulfing and subsequently destroying them. Alcohol interferes with the function of the monocyte-macrophage system, with clinically significant consequences. For example, compared with healthy people, alcoholics are less resistant to infections by microorganisms that normally are eradicated by monocytes”

“and macrophages, such as the bacteria that cause tuberculosis and various forms of pneumonia.”

“ Thus, in alcoholic patients whose monocyte-dependent elimination of a defective form of albumin (aprotein normally present in the blood) is reduced at admission to a hospital, monocyte function generally returns to normal within 1 week of abstinence from alcohol. Further studies indicate that alcohol impairs monocyte/macrophage function rather than production. Thus, the cells frequently remain at their normal locations in the tissues rather than migrate to the sites of infections.In addition, alcohol inhibits the monocytes’ adhesion abilities.”

ALCOHOL’S EFFECTS ON THE BLOOD-CLOTTING SYSTEM

“Blood clotting, or coagulation, an important physiological process that ensures the integrity of the vascular system, involves the platelets, or thrombocytes, as well as several proteins dissolved in the plasma. When a blood vessel is injured, platelets are attracted to the site of the injury, where they aggregate to form a temporary plug. The platelets secrete several proteins (i.e., clotting factors) that—together with other proteins either secreted by surrounding tissue cells or present in the blood—initiate a chain of events that results in the formation of fibrin. Fibrin is a stringy protein that forms a tight mesh in the injured vessel; blood cells become trapped in this mesh, thereby plugging the wound. Fibrin clots,”

“in turn, can be dissolved by a process that helps prevent the development of thrombosis (i.e., fibrinolysis). Alcohol can interfere with these processes at several levels, causing, for example, abnormally low platelet numbers in the blood(i.e.,thrombocytopenia), impaired platelet function(i.e., thrombocytopathy), and diminished fibrinolysis. These effects can have serious medical consequences, such as an increased risk for strokes.”

Thrombocytopenia

“Thrombocytopenia is a frequent complication of alcoholism, affecting 3 to 43 percent of nonacutely ill, wellnourished alcoholics and 14 to 81 percent of acutely ill, hospitalized alcoholics. Thus, apart from acquired immune deficiency syndrome (AIDS), alcoholism probably is the leading cause of thrombocytopenia. Except for the most severe cases, however, the patients generally do not exhibit manifestations of excessive bleeding.Moreover, alcohol-related thrombocytopenia generally is transient, and platelet counts usually return to normalwithin 1 week of abstinence.Therefore, patients generally require no therapeutic intervention other than that needed to ease alcohol withdrawal. Only in patients whose thrombocytopenia is severe and associated with excessive bleeding are platelet transfusions indicated. In many patients with thrombocytopenia, rebounding platelet numbers even exceed normal”

“values. This rebound thrombocytosis after cessation of alcohol consumption also occurs in the majority of patients whose platelet counts are normal at the time of hospitalization. In these patients, the extent of the excess in circulating platelets usually is higher than in patients presenting with thrombocytopenia. “

“The exact mechanisms underlyingalcohol-related thrombocytopenia remain unknown. Some researchers have suggested that alcohol intoxication itself, rather than alcohol-related nutritional deficiencies, causes the decrease in platelet numbers. This view is supported by findings that thrombocytopenia developed in healthy subjects who received a diet containing adequate protein and vitamin levels (including large doses of folic acid) and consumed the equivalent of 1.5 pints (i.e., 745 milliliters) of 86-proof whiskey for at least 10 days (Lindenbaum 1987). The subjects’ platelet levels returned to normal when alcohol consumption was discontinued. Similarly, platelet counts can be reduced in well-nourished alcoholics who do not suffer from folic acid deficiency. The available data also suggest that alcohol can interfere with a late stage of platelet production as well as shorten the life span of existing platelets. Individual drinkers appear to differ in their susceptibility to alcohol-induced thrombocytopenia. Thus, clinicians have noted that some people who consume alcohol in excess repeatedly develop thrombocytopenia (often severely), whereas other drinkers”

“maintain normal platelet levels. In addition to differences in the quantity of alcohol consumed, inherited or acquired variations in an individual drinker’s biochemistry may account for these differences in susceptibility.”

Thrombocytopathy

“Alcohol affects not only platelet production but also platelet function. Thus, patients who consume excessive amounts of alcohol can exhibit a wide spectrum of platelet abnormalities, These include impaired platelet aggregation, decreased secretion or activity of platelet-derived proteins involved in blood clotting, and prolongation of bleeding in the absence of thrombocytopenia. Because alcohol impairs the function of the normal blood-clotting system, it also can adversely interact with over-the-counter and prescription medications that prolong bleeding or prevent coagulation. The concomitant use of alcohol and aspirin or NSAID’s greatly increases the patient’s risk for gastrointestinalbleeding. Similarly, alcohol can enhance aspirin-induced fecal blood loss.”

HEMATOGICAL MARKERS OF ALCOHOLISM

State Markers

“Chronic ingestion of large quantities of alcohol alters many physiological andbiological processes and compounds, including several blood-related (i.e., hematological) variables. Because blood samples are”

“relatively easy to obtain, structural and functional changes in circulating blood cells and plasma proteins potentially can form the basis of laboratory tests for screening, diagnosing, and monitoring alcoholism. Two hematological state markers commonly used for these purposes are the presence of carbohydrate-deficient transferring (CDT) in the blood and an increase in the size of red blood cells (RBC’s), as measured by the mean corpuscular volume (MCV).”

Carbohydrate-Deficient Transferrin.

“CDT is one of the newest—and perhaps the most promising—of thehematological state markers. Transferrin is an iron-containing protein in the plasma that transports iron, which is stored at various sites in the body, to the developing RBC’s in the bone marrow for incorporation into hemoglobin. Transferrin molecules in the blood usually contain several carbohydrate components. In chronic heavy drinkers, however, the number of carbohydrate components in each transferring molecule is reduced, resulting in CDT. The mechanism underlying this alteration still is unclear.”

“Because elevated CDT levels in the blood appear to be a specific consequence of excessive alcohol consumption, a recent study investigated the utility of repeatedly monitoring serum CDT to detect relapse among recovering alcoholics. The study found that in most of the”

“subjects who relapsed, the elevation of CDT levels preceded self-reported alcohol consumption by at least 28 days. These findings suggest that repeated testing of alcoholic patients for CDT permits early relapse detection and thus may lead to early intervention. Early intervention, in turn, may decrease the need to rehospitalize patients for alcohol withdrawal and prevent some of the complications associated with sustained excessive drinking. **“**

MATERIALS AND METHODS

Setting:

Department of Medicine,

GovtRajaji Hospital,Madurai Medical College,Madurai.

Inclusion criteria

Age 20-40 yr

Alcohol consumption 210 gms of ethanol/week in males & 100gm of ethanol/week in females for minimum of one year

Exclusion criteria:

Patients with

- Liver disease
- Viral hepatitis
- Renal disease
- Known Thyroid disease
- Hematological malignancies
- h/o drug intake that alter hematological profile
- Immunosuppressed individuals
- Other co-morbid illness

DESIGN OF STUDY

Prospective observational study.

PERIOD OF STUDY

6 Months from November 2015 to April 2016

PARTICIPANTS

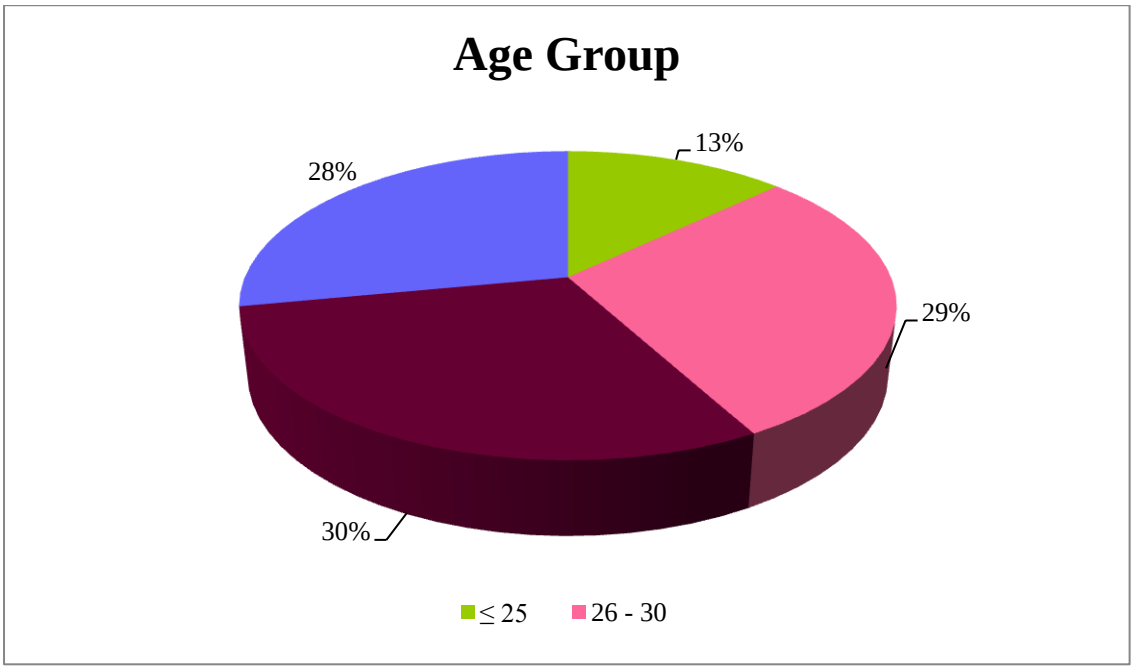
100 patients in the age group of 20-40 years with history of alcohol consumption 210 gms/week in males & 100 gms /week in females for minimum one year admitted with another primary admitting diagnosis in Department of Medicine,Government Rajaji hospital

METHOD

- 100 patients admitted in medical ward with another primary diagnosis are selected based on the inclusion/exclusion criteria & history is obtained from each patient based on the previously prepared proforma& clinical examination
- USG abdomen & pelvis ,viral markers will be done to rule out pre existing alcoholic liver disease ,blood samples collected &sent for complete hemogram,peripheralsmear,serum B12 assay will be done in all patients to screen for pre existing B12 deficiency

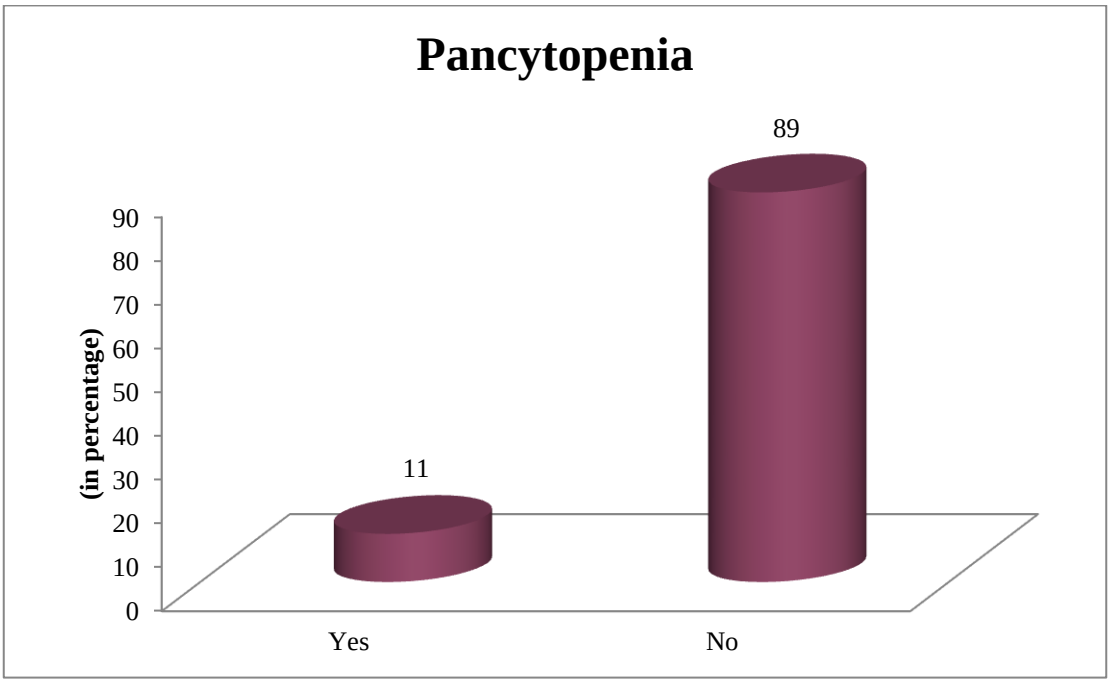
OBSERVATION & RESULTS

Age group (in yrs)	Number	Percentage
≤ 25	13	13.0
26 – 30	29	29.0
31 – 35	30	30.0
36 – 40	28	28.0
Total	100	100.0



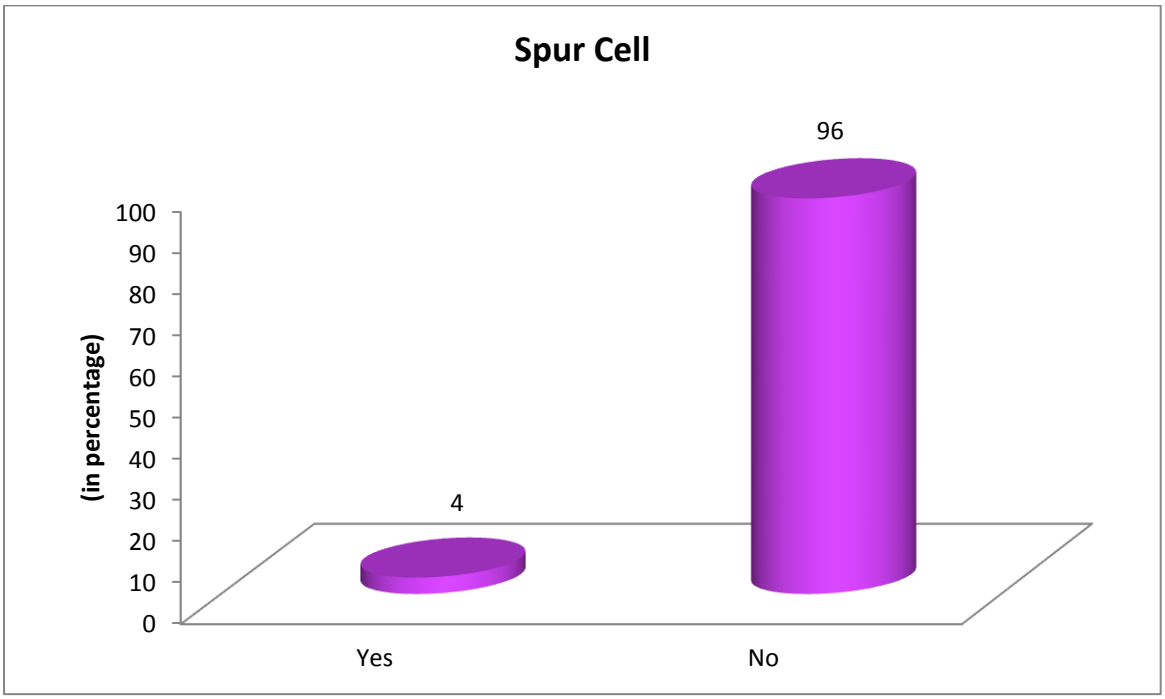
100 Patients included in the study 13% are < 25 years of age,29% are between 26-30 years,30% between 31-35 years,28& are between 36-40 years

Pancytopenia	Number	Percentage
Yes	11	11.0
No	89	89.0
Total	100	100.0

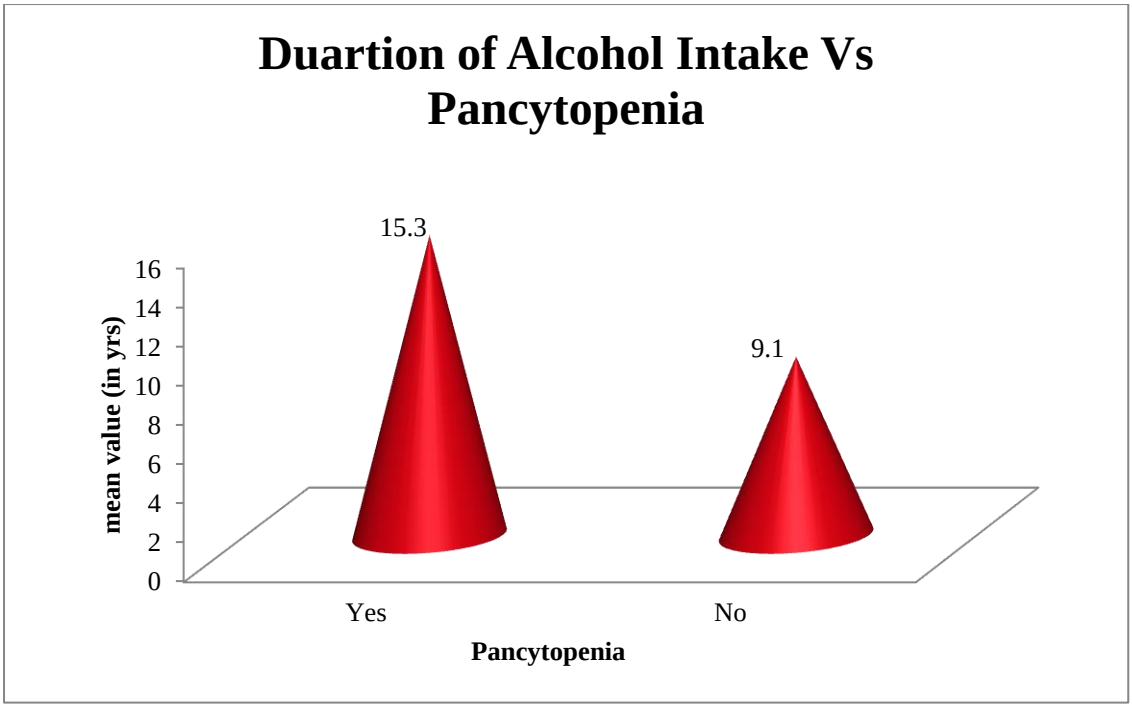


Of the 100 Patients 11% had Pancytopenia

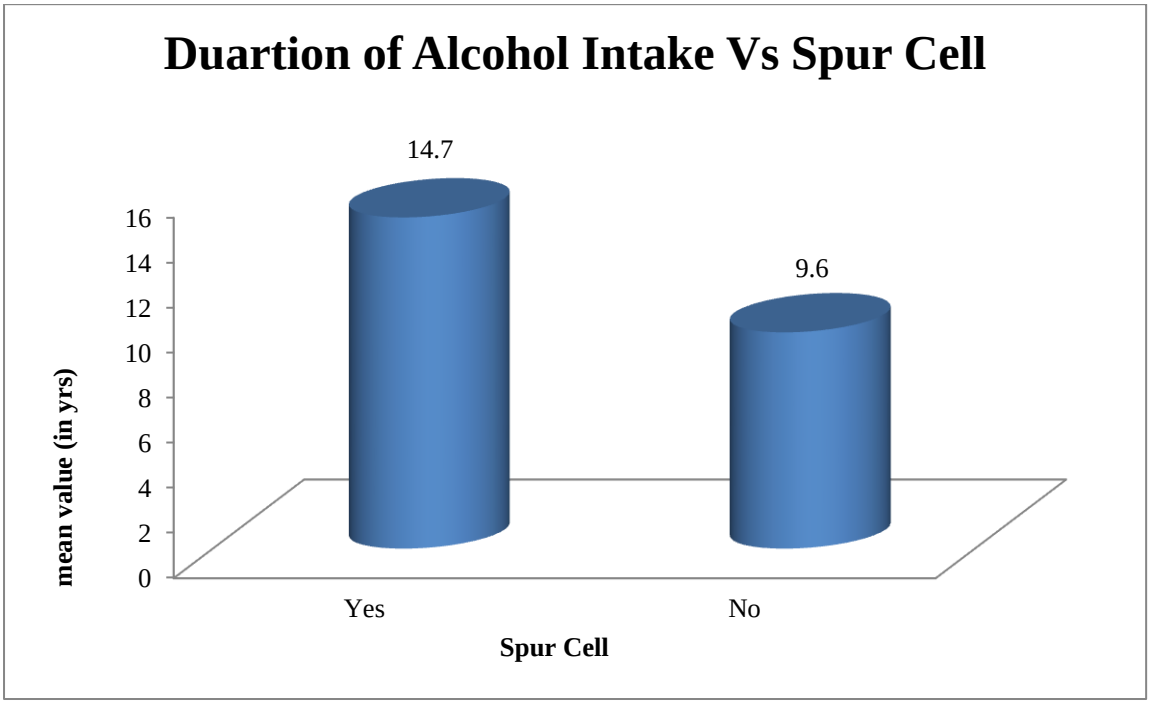
Spur Cell	Number	Percentage
Yes	4	4.0
No	96	96.0
Total	100	100.0

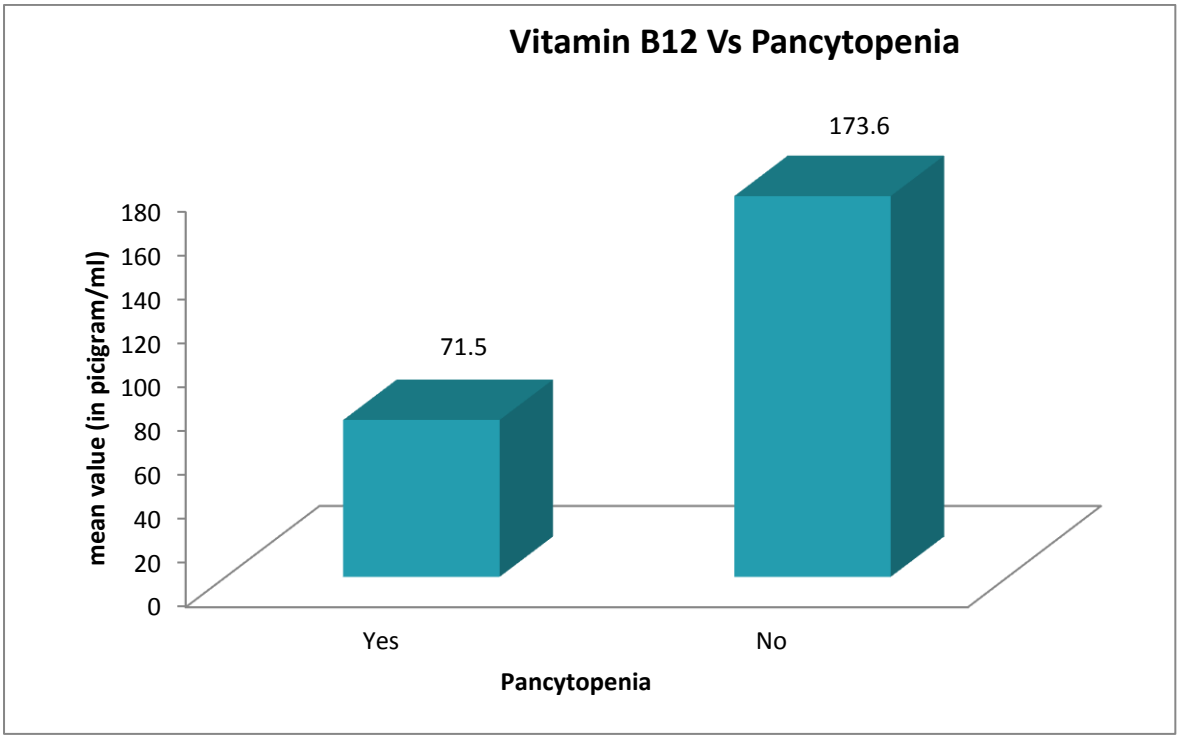


4% had Spur cells in their Peripheral smear out of 100 patients



As the duration of alcohol increases the incidence of Pancytopenia & presence of spur cells increases



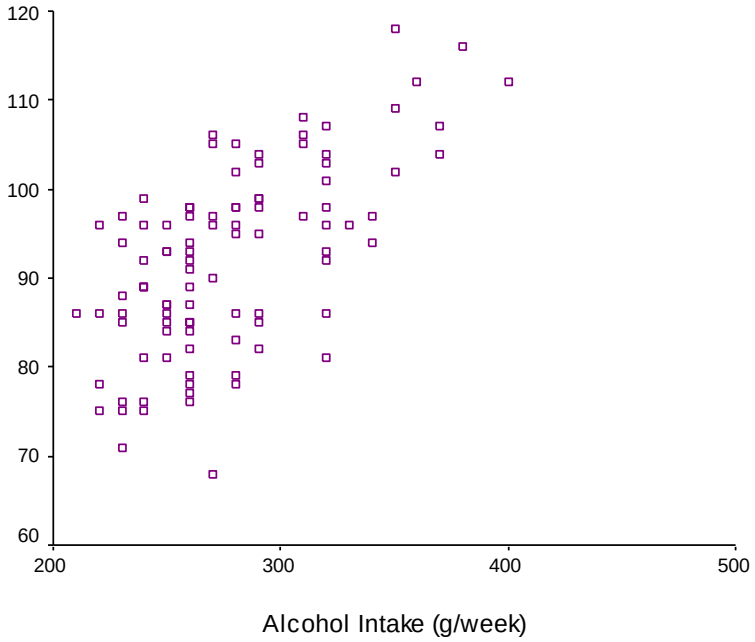


As the duration of alcohol & quantity of consumption increases serum B12 values decreases, as the B12 value decreases the incidence of Pancytopenia increases,hence the incidence of Pancytopenia has positive correlation both to duration & quantity of aslcohol intake

Correlation between alcohol intake and CDT

	Mean	Standard Deviation	Correlation Co-efficient	p-value
Alcohol Intake (g/week)	276.9	40.3	0.632	<0.001
Carbohydrate Deficient Tranferrin (mg/dl)	92.1	10.4		

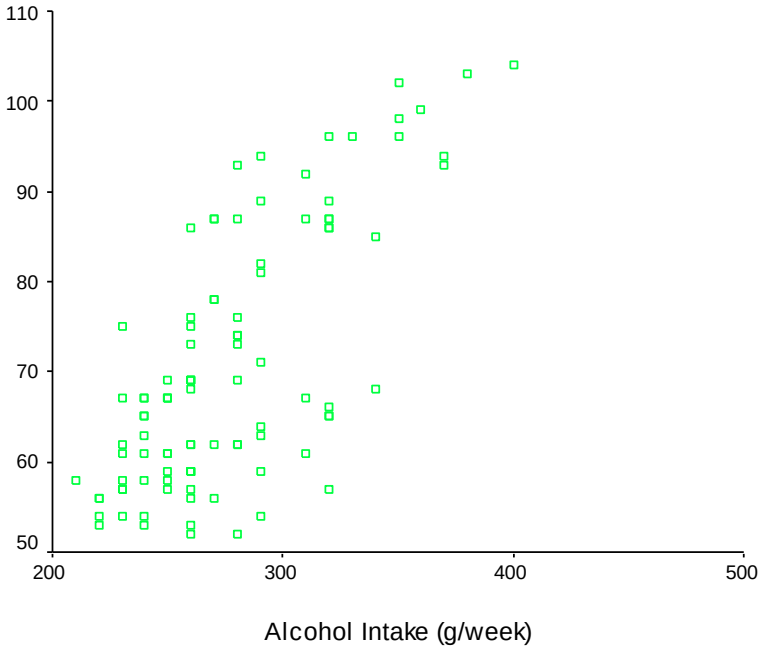
Fig 1: Scatter plot diagram of alcohol intake Vs CDT



Correlation between alcohol intake and GGT

	Mean	Standard Deviation	Correlation Co-efficient	p-value
Alcohol Intake (g/week)	276.9	40.3	0.726	<0.001
Gamma GlutamylTranspeptidase (u/l)	70.7	14.2		

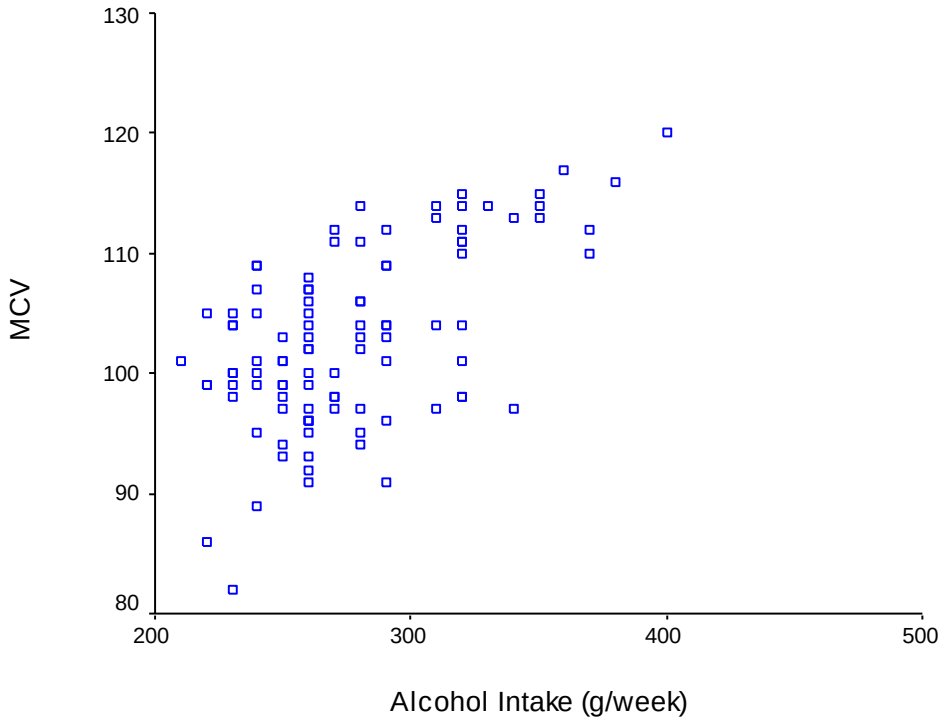
Fig 2: Scatter plot diagram of alcohol intake Vs GGT



Correlation between alcohol intake and MCV

	Mean	Standard Deviation	Correlation Co-efficient	p-value
Alcohol Intake (g/week)	276.9	40.3	0.587	<0.001
MCV	103.0	7.4		

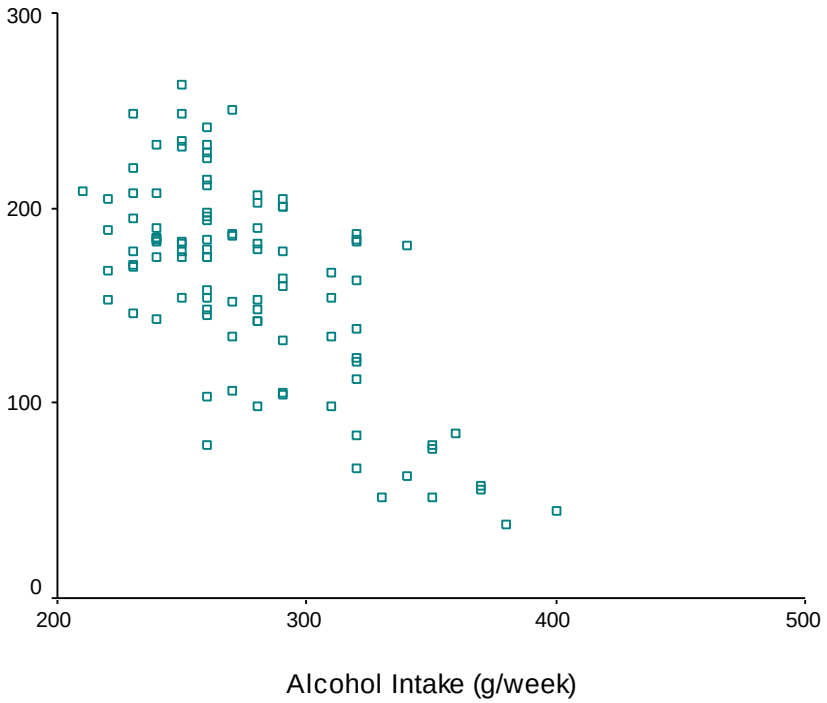
Fig 3: Scatter plot diagram of alcohol intake Vs MCV



Correlation between alcohol intake and Vitamin B12

	Mean	Standard Deviation	Correlation Co-efficient	p-value
Alcohol Intake (g/week)	276.9	40.3	-0.684	<0.001
Vitamin B12 (pictogram/ml)	162.4	52.1		

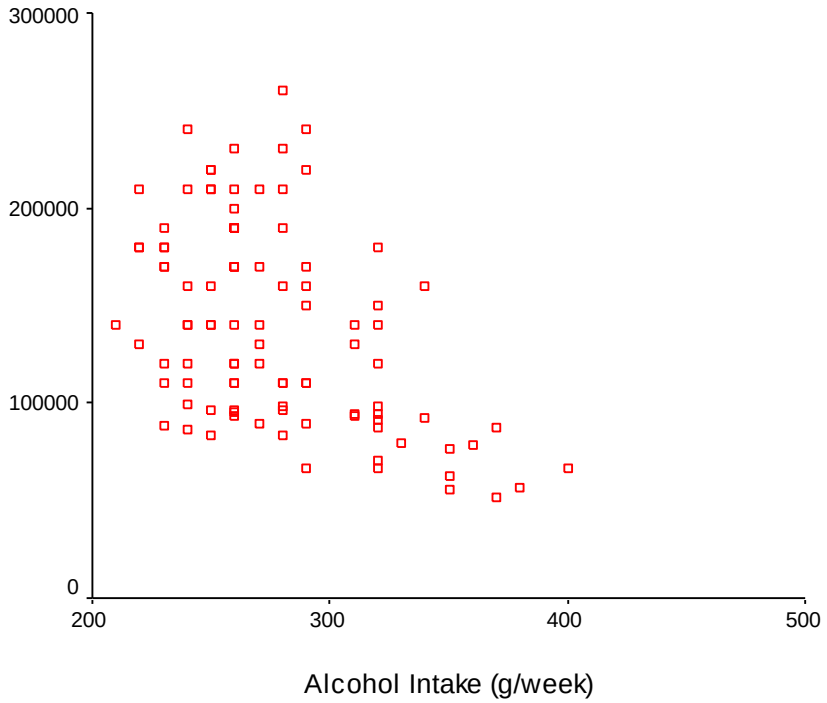
Fig 4: Scatter plot diagram of alcohol intake Vs Vitamin B12



Correlation between alcohol intake and Platelet Count

	Mean	Standard Deviation	Correlation Co-efficient	p-value
Alcohol Intake (g/week)	276.9	40.3	-0.477	<0.001
Platelet Count (in lakhs/cubic mm)	139600.0	51340.2		

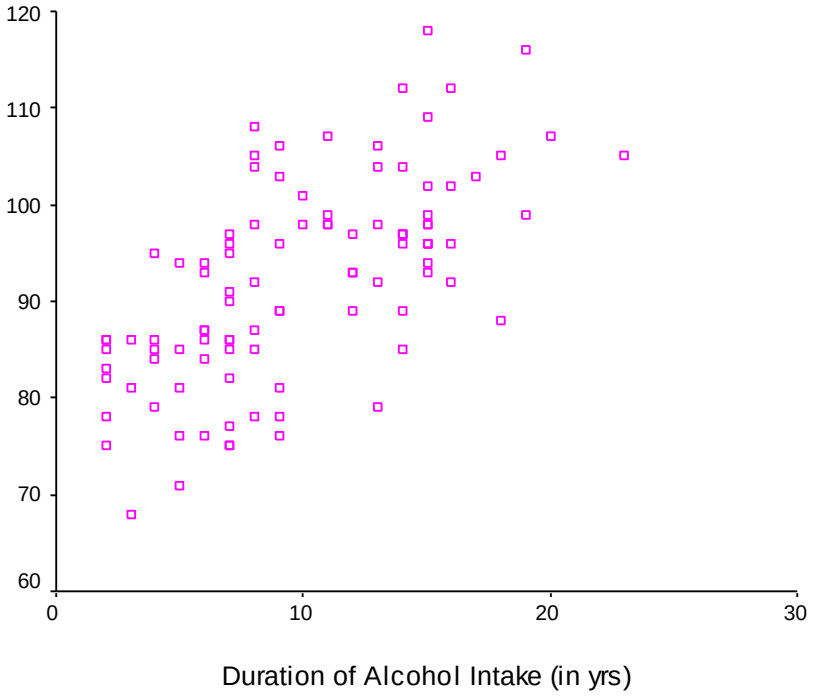
Fig 5: Scatter plot diagram of alcohol intake Vs Platelet Count



Correlation between duration of alcohol intake and CDT

	Mean	Standard Deviation	Correlation Co-efficient	p-value
Duration of Alcohol Intake (in yrs)	9.8	4.9	0.645	<0.001
Carbohydrate Deficient Tranferrin (mg/dl)	92.1	10.4		

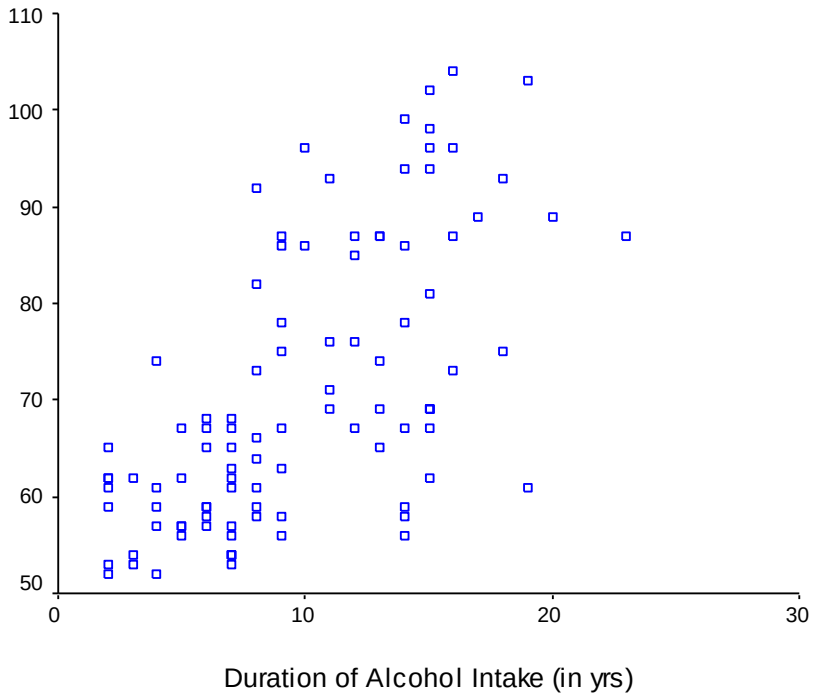
Fig 6: Scatter plot diagram of duration of alcohol intake Vs CDT



Correlation between duration of alcohol intake and GGT

	Mean	Standard Deviation	Correlation Co-efficient	p-value
Duration of Alcohol Intake (in yrs)	9.8	4.9	0.634	<0.001
Gamma GlutamylTranspeptidase (u/l)	70.7	14.2		

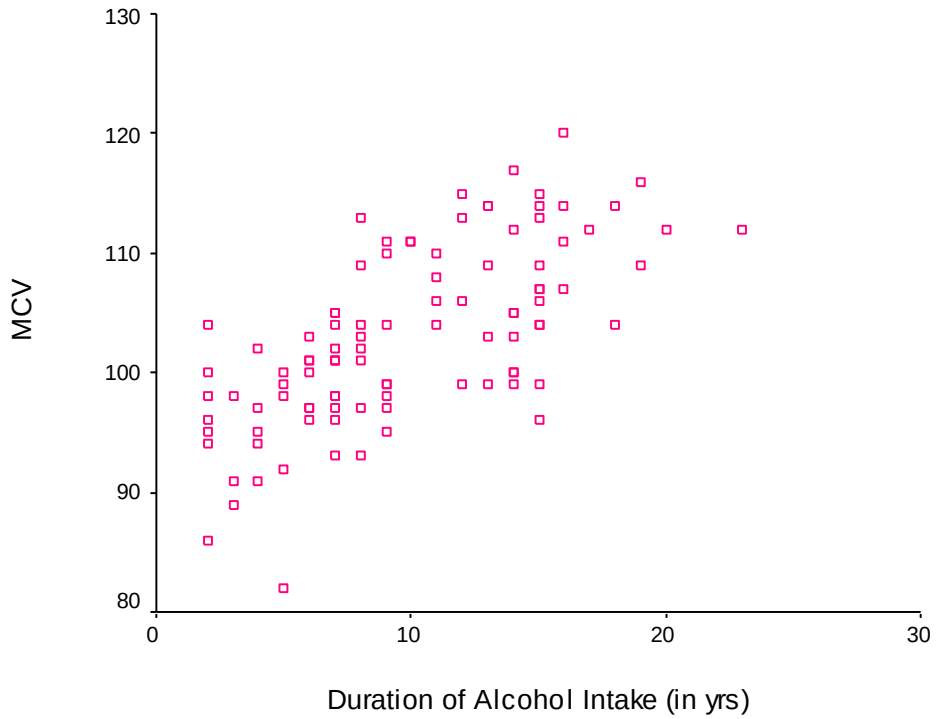
Fig 7: Scatter plot diagram of duration of alcohol intake Vs GGT



Correlation between duration of alcohol intake and MCV

	Mean	Standard Deviation	Correlation Co-efficient	p-value
Duration of Alcohol Intake (in yrs)	9.8	4.9	0.680	<0.001
MCV	103.0	7.4		

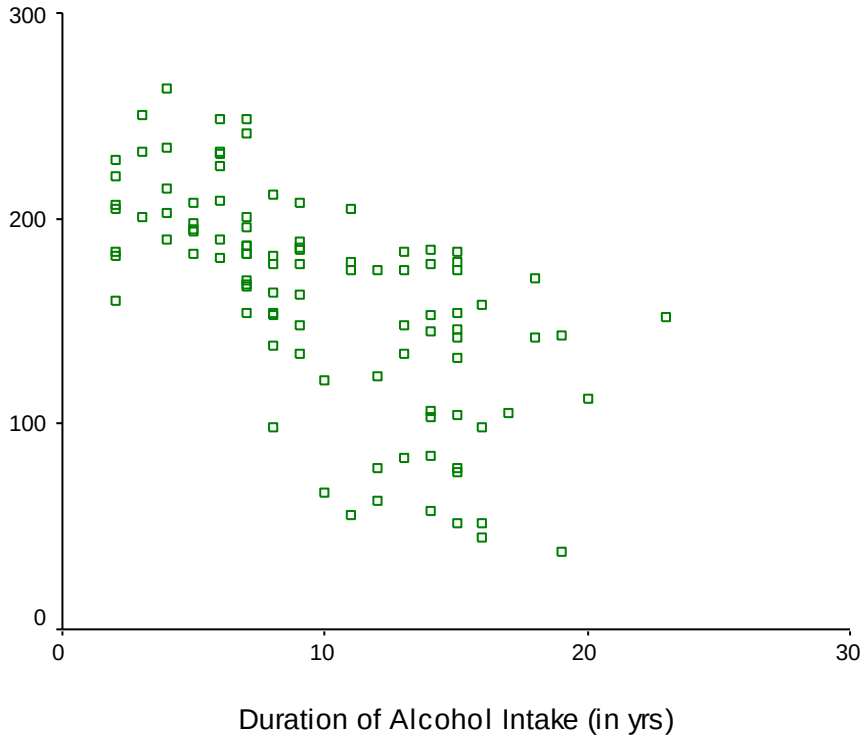
Fig8: Scatter plot diagram of duration of alcohol intake Vs MCV



Correlation between duration of alcohol intake and Vitamin B12

	Mean	Standard Deviation	Correlation Co-efficient	p-value
Duration of Alcohol Intake (in yrs)	9.8	4.9	-0.650	<0.001
Vitamin B12 (pictogram/ml)	162.4	52.1		

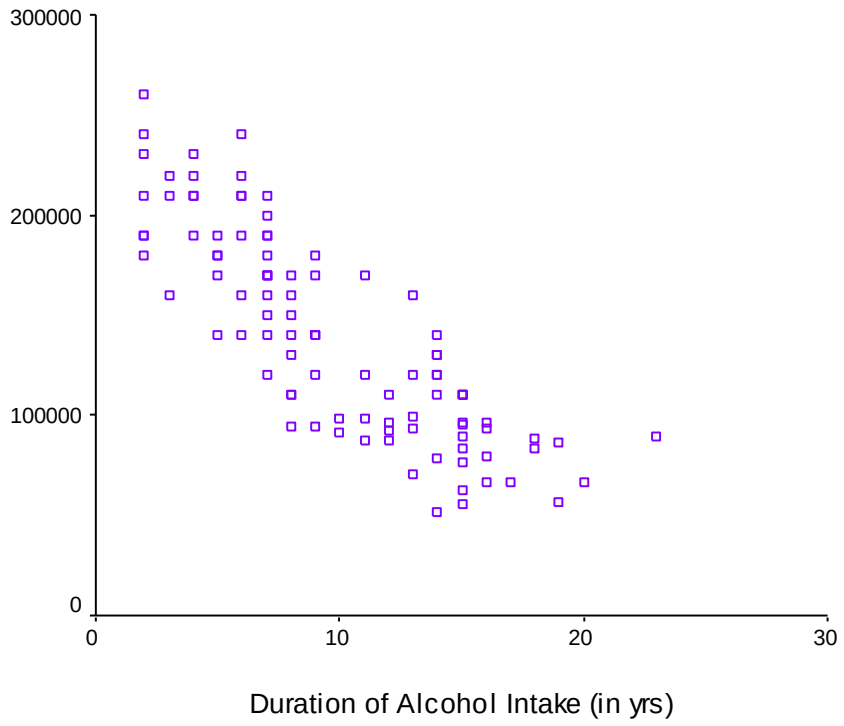
Fig 9: Scatter plot diagram of duration of alcohol intake Vs Vitamin B12



Correlation between alcohol intake and Platelet Count

	Mean	Standard Deviation	Correlation Co-efficient	p-value
Duration of Alcohol Intake (in yrs)	9.8	4.9	-0.836	<0.001
Platelet Count (in lakhs/cubic mm)	139600.0	51340.2		

Fig 10: Scatter plot diagram of duration of alcohol intake Vs Platelet Count



	Pancytopenia			
	Yes		No	
	N=11		N=89	
	Mean	SD	Mean	SD
Vitamin B12 (picogram/ml)	71.5	23.9	173.6	42.8
p-value	P<0.001 (Significant)			

	Spur Cell			
	Yes		No	
	N=4		N=96	
	Mean	SD	Mean	SD
Duration of Alcohol Intake (in yrs)	14.7	0.9	9.6	4.8
p-value	P=0.039 (Significant)			

DISCUSSION

In our study we included 100 patients after applying inclusion & exclusion criteria,short history & clinical examination are done in all patients. all the patients were screened for serum B12 levels,MCV,Peripheralsmear,CDT,GGT values are done in all patients.

In our study we included 100 patients between 20-40 years of age, incidentally all of them are males,13% are less than or equal to 25 years,29% are between 26-30 years of age,30% between 31-35 years & 28 % are between 36-40 years of age.In the 100 patients we enquired about their drinking habits & looked for MCV,GGT,CDT,Spur cells & Pancytopenia in peripheral smear,serum B12 levels,11% had pancytopenia & 4% had spurcells in peripheral smear which are statistically significant,

As the duration of alcohol increases the incidence of pancytopenia & presence of spur cells increases.As the duration of alcohol & quantity of consumption increases serum B12 values decreases, as the B12 value decreases the incidence of Pancytopenia increases,hence the incidence of Pancytopenia has positive correlation both to duration & quantity of aslcoholintake.There is a significant positive correlation between quantity & duration of alchol intake & rise in CDT levels.

There is a significant positive correlation between quantity &duration ofalchol intake & rise in CDT levels.MCV rises as the duration & quantity of alcohol intake increases which is independent of serum B12 levels.As the quantity & duration of alcohol intake increases the serum B12 levels & Platelet count decreases.

LIMITATIONS OF THE STUDY

This study has its own limitation. The number of patients in this study is small. Hence generalizations of results of the study have to be made withcaution. The study population involved patients seeking medical care in our hospital which is a tertiary care center and hence they may not represent the general population.

SUMMARY

- In our study we included 100 patients between 20-40 years of age, incidentally all of them are males,13% are less than or equal to 25 years,29% are between 26-30 years of age,30% between 31-35 years & 28 % are between 36-40 years of age
- In the 100 patients we enquired about their drinking habits & looked for MCV,GGT,CDT,Spur cells & Pancytopenia in peripheral smear,serum B12 levels
- 11% had pancytopenia & 4% had spurcells in peripheral smear which are statistically significant
- As the duration of alcohol increases the incidence of pancytopenia & presence of spur cells increases
- As the duration of alcohol & quantity of consumption increases serum B12 values decreases, as the B12 value decreases the incidence of Pancytopenia increases,hence the incidence of Pancytopenia has positive correlation both to duration & quantity of aslcohol intake
- There is a significant positive correlation between quantity & duration of alchol intake & rise in CDT levels
- There is a significant positive correlation between quantity & duration of alchol intake & rise in CDT levels

- MCV rises as the duration & quantity of alcohol intake increases which is independent of serum B12 levels
- As the quantity & duration of alcohol intake increases the serum B12 levels & Platelet count decreases

CONCLUSION

“Alcohol has numerous adverse effects on the various types of blood cells and their functions. For example, heavy alcohol consumption can cause generalized Suppression of blood cell production resulting in Pancytopenia & thrombocytopenia and the production of structurally abnormal blood cell precursors like spur cells that cannot mature into functional cells,apart from that there is a significant rise in CDT ,GGT levels & also there is rise in MCV both megaloblastic& non megaloblasticmacrocytosis occurs in significant percentage with the reduction in serum B12 levels, hence these parameters could be considered as markers of alcohol abuse.Due to the limited sensitivity of any single laboratory marker, the parallel measurement of CDT with traditional alcohol markers may enhance the ability to detect alcohol abuse.studies indicate that thecombined measurement of CDT and GGT or of CDT and MCV could achieve such an enhancement”

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LIST OF ABBREVATIONS :

CDT : Carbohydrate Defecient Transferrin

MCV : Mean Corpuscular Volume

GGT : Gamma Glutamyl Transpeptidase

PROFORMA:

Name: Age / Sex: Occupation:

Presenting complaints:

Past History:

H/o DM, HT, CKD, CVD, DRUG INTAKE, CAD, Thyroid disorders,drug intake

Personal history : smoker - yes / no

If yes - Duration :

Alcoholic - yes / no

If yes - Duration :

Clinical Examination:

General Examination:

Consciousness, Pallor, jaundice, Clubbing, Lymphadenopathy

Vitals: Pulse Rate: Blood pressure: Respiratory Rate: SpO2:

Systemic examination: CVS: RS: ABDOMEN: CNS:

Laboratory investigations:

Complete hemogram

Peripheral smear

Fasting lipid profile

Liver function tests,CDT

Prothrombin time,INR

USG abdomen & pelvis

S.no	Age/Sex	Alcohol intake g	Duration	CDT	GGT	MCV	Vit B12	Platelet count	Pancytopenia	spur cells
1	25	220	7	86	54	105	168	180000	N	N
2	34	400	16	112	104	120	45	67000	Y	Y
3	36	350	15	102	98	115	76	76000	Y	N
4	34	260	12	89	76	106	78	110000	N	N
5	29	320	10	98	86	111	67	98000	N	N
6	25	280	2	78	62	104	182	190000	N	N
7	29	230	7	75	54	105	170	170000	N	N
8	31	340	12	97	85	113	63	92000	N	N
9	30	370	11	107	93	110	56	87000	Y	N
10	25	280	4	95	74	102	203	210000	N	N
11	29	240	6	76	65	100	190	240000	N	N
12	35	260	14	85	86	103	103	140000	N	N
13	36	330	16	96	96	114	52	79000	N	N
14	32	370	14	104	94	112	58	52000	Y	Y
15	40	380	19	116	103	116	38	57000	Y	N
16	34	320	12	93	87	115	123	87000	N	N
17	30	260	9	76	75	104	148	170000	N	N
18	31	220	9	78	56	99	189	180000	N	N
19	28	260	7	77	68	102	154	200000	N	N
20	29	320	8	92	66	101	138	150000	N	N
21	35	270	14	97	78	100	106	130000	N	N
22	28	250	9	81	67	98	178	140000	N	N
23	23	290	2	82	59	96	160	240000	N	N
24	29	240	7	75	54	101	183	210000	N	N
25	39	280	13	79	74	103	148	160000	N	N
26	27	230	5	71	67	99	208	180000	N	N
27	25	270	3	68	62	98	250	210000	N	N
28	29	260	8	78	59	102	212	170000	N	N
29	32	310	13	106	87	114	134	93000	N	N
30	33	220	14	96	56	99	153	130000	N	N
31	37	230	15	94	62	104	146	110000	N	N
32	31	280	11	98	76	106	179	98000	N	N
33	25	250	4	85	57	94	234	210000	N	N
34	26	260	7	82	53	96	241	190000	N	N
35	29	290	11	99	71	104	205	170000	N	N
36	33	240	15	96	67	107	184	110000	N	N
37	36	260	15	93	69	96	175	96000	N	N
38	40	270	23	105	87	112	152	89000	N	N
39	29	320	7	96	65	104	187	120000	N	N
40	26	260	7	91	62	93	196	190000	N	N
41	25	340	6	94	68	97	181	160000	N	N
42	27	240	9	89	63	95	208	140000	N	N
43	34	250	12	93	67	99	175	96000	N	N
44	37	290	15	99	81	104	132	110000	N	N
45	35	260	16	92	73	107	158	93000	N	N
46	36	240	14	89	67	105	185	120000	N	N

47	39	230	18	88	75	104	171	88000	N	N
48	27	260	6	87	59	96	232	210000	N	N
49	38	320	20	107	89	112	112	67000	Y	N
50	29	250	6	87	67	101	248	220000	N	N
51	25	280	2	83	62	94	207	260000	N	N
52	36	230	14	97	58	100	178	120000	N	N
53	27	260	2	85	52	95	228	230000	N	N
54	29	320	5	81	57	98	183	140000	N	N
55	37	260	15	98	69	107	179	95000	N	N
56	39	240	19	99	61	109	143	86000	N	N
57	32	210	6	86	58	101	209	140000	N	N
58	34	230	7	85	57	98	248	170000	N	N
59	31	290	7	95	63	101	201	150000	N	N
60	35	260	13	98	69	99	184	120000	N	N
61	36	350	15	118	96	113	78	56000	Y	N
62	25	320	2	86	65	98	184	180000	N	N
63	27	260	4	79	59	91	215	190000	N	N
64	29	250	8	87	58	93	182	140000	N	N
65	37	280	15	96	69	106	142	110000	N	N
66	39	240	13	92	65	109	175	99000	N	N
67	31	250	7	86	61	101	183	160000	N	N
68	35	240	9	89	58	99	185	140000	N	N
69	29	260	6	84	57	97	225	190000	N	N
70	26	290	3	86	54	91	201	220000	N	N
71	28	270	7	90	56	98	187	170000	N	N
72	25	280	4	86	52	95	190	230000	N	N
73	36	250	15	96	69	99	154	83000	N	N
74	31	320	9	103	86	110	163	94000	N	N
75	40	260	14	97	59	105	145	110000	N	N
76	32	310	8	105	61	104	154	130000	N	N
77	34	320	10	101	96	111	121	91000	N	N
78	38	360	14	112	99	117	84	78000	Y	Y
79	40	280	18	105	93	114	142	83000	N	N
80	28	230	5	76	57	82	195	180000	N	N
81	24	220	2	75	53	86	205	210000	N	N
82	29	250	4	84	61	97	263	220000	N	N
83	31	290	8	85	64	103	178	160000	N	N
84	34	310	7	97	67	97	167	140000	N	N
85	28	260	5	85	56	92	194	170000	N	N
86	25	240	3	81	53	89	232	160000	N	N
87	37	290	17	103	89	112	105	67000	Y	N
88	31	270	9	96	78	97	134	140000	N	N
89	32	280	8	98	73	97	153	110000	N	N
90	35	320	13	104	87	114	83	71000	Y	N
91	39	350	15	109	102	114	52	63000	Y	Y
92	40	310	8	108	92	113	98	94000	N	N
93	34	270	9	106	87	111	186	120000	N	N

94	38	290	8	104	82	109	164	110000	N	N
95	29	260	5	94	62	100	198	190000	N	N
96	31	250	6	93	59	103	231	210000	N	N
97	38	280	16	102	87	111	98	96000	N	N
98	40	290	15	98	94	109	104	89000	N	N
99	25	230	2	86	61	100	221	190000	N	N
100	37	260	11	98	69	108	175	120000	N	N

MADURAI MEDICAL COLLEGE
MADURAI, TAMILNADU, INDIA -625 020
(Affiliated to The Tamilnadu Dr.MGR Medical University, Chennai, Tamil Nadu)

ETHICS COMMITTEE CERTIFICATE

Name of the Candidate	:	Dr.P.Thirunavukarasu
Course	:	PG in MD., General Medicine
Period of Study	:	2014-2017
College	:	MADURAI MEDICAL COLLEGE
Research Topic	:	Study of Hematological abnormalities in alcoholics
Ethical Committee as on	:	27.07.2016

The Ethics Committee, Madurai Medical College has decided to inform that your Research proposal is accepted.

Member Secretary Chairman Dean / Convenor

DEAN
Madurai Medical College
Madurai-20

06 SEP 2016

INTRODUCTION

"Alcohol consumption has increased considerably in the past 25 years,the need for accurate methods for detection and monitoring of alcohol related problems in different health care settings is clearly considerable.Despite such a need, there is no exact clinical finding or symptom in a patient history,that is sufficiently sensitive and specific to detect alcohol related problem in its early phase."

"The clinical signs of alcohol abuse are rather minimal in the early phase of this process while most of the signs arise later after several years of excessive drinking. Also alcohol consumption is usually under-reported in interviews; alcohol abusers tend to underestimate their drinking even more than the social drinkers.The reasons for using biological laboratory markers are that they give objective information about alcohol consumption and changes in drinking habits. Among these laboratory markers haematological abnormalities appear earlier than biochemical abnormalities & also reversible with abstinence."

"Alcohol effect on hematopoeitic system are both direct & indirect, its also dose dependent, The direct consequences of excessive alcohol consumption include toxic effects on the bone marrow; suppress the production of all blood cell precursors. Alcohol's indirect effects include"

"nutritional deficiencies that impair the production and function of various blood cells. Among the hematological abnormalities, increased MCV values have been observed in 64-89% of alcohol abusers.Increased MCV values are also found in cases of vitamin B12 and folic acid deficiency, liver diseases, several hematological disorders,hypothyroidism,in users of anti-epileptics. Alcohol abuse has been found to explain increased MCV values in 89% of men and 56% of

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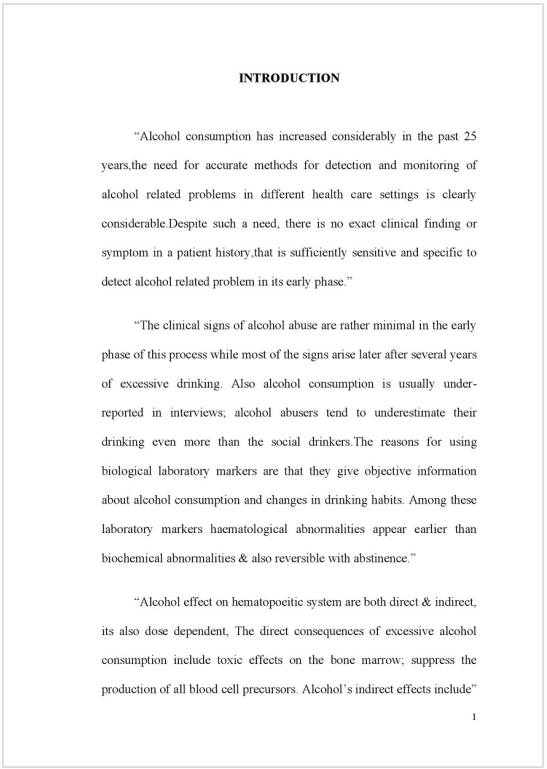

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